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Executive Functions and Brain Volumes in Children with Congenital Heart Disease and Very Preterm Children

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Abstract

Children with congenital heart disease (CHD) and very preterm children are at high risk for impairments in the executive functions (EF). Searching for the underlying neuronal correlates, reduced volumes were found in both groups, particularly in the subcortical brain structures. Although the two groups show a very similar profile of EF deficits and reduced brain volumes, to date they have not been compared directly in any previous studies. The aim of this master's thesis was to investigate, if and to what extent children with CHD differ from very preterm children. A third group of healthy term-born children acted as a control group. 45 children aged between 9 and 11 years were examined for their working memory, cognitive flexibility and visual-spatial planning, assessed with commonly applied cognitive tests. Brain volumes were evaluated through magnetic resonance imaging (MRI) and the images were analyzed using an automated regional segmentation tool (FreeSurfer). Children with CHD and very preterm children were significantly worse in the Corsi Block Tapping Task, assessing visual-spatial working memory, compared to the control group. Whereas children with CHD had smaller volumes in the left cerebellar white matter and in the right caudate nucleus compared to the controls, children born very preterm exhibited smaller volumes in the ventrolateral prefrontal cortex than the controls. Positive correlations between poorer working memory performance and subcortical brain volumes were only found for the very preterm children, indicating different neuronal underpinnings for EF deficits in children with CHD and very preterm children.

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1. Introduction

Cognitive abilities are crucial for living a successful independent life (e.g., having academic success but also possessing an appropriately behavior in day-to-day interactions with others). The healthy development of these abilities is crucial for physical and psychological health. Particularly, higher cognitive processes – the executive functions – are important for such a successful life. Executive functions develop during childhood and adolescence. But is it a given that all the humans fully develop these fundamental higher functions? What about individuals who did not have an easy start in their life?

Congenital heart disease occurs in 10 to 12 out of 1'000 live births (Hoffman, 2013) and is therefore one of the most common congenital diseases in the world (Hoffman & Kaplan, 2002). Most of the affected people (80% - 90%) now survive into adulthood due to the progress in medicine (Wernovsky, 2008). However, these patients are at high risk for impairments in executive functions (Cassidy, White, DeMaso, Newburger, & Bellinger, 2015; von Rhein et al., 2015).

Similar findings exist for individuals born preterm. In their meta-analysis, Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan (2009) demonstrated that preterm-born individuals show moderate to severe deficits in their executive functions. In Switzerland seven to eight out of 100 live births are preterm (Bundesamt für Statistik, 2010). This means many adolescents live with a higher risk for impaired development of their executive functions.

In addition to these findings about deficits in executive functions, these two clinical groups also show some alterations in their brain structure. Von Rhein, Buchmann, et al. (2015) revealed that children with severe congenital heart disease exhibit reduced global and regional brain volumes. Corresponding results also exist for preterm children (Nosarti et al., 2008; de Kieviet, Zoetebier, van Elburg, Vermeulen & Oosterlaan, 2012).

Von Rhein et al. (2014) demonstrated that reduced brain volumes in children with congenital heart disease are associated with executive function deficits in children with congenital heart disease. There are also some studies showing a similar correlation between reduced brain volumes and neuropsychological deficits in children born preterm (Nosarti et al., 2008; de Kieviet et al., 2012).

Although the findings for these two clinical groups are quite similar, to date they have not been compared directly in any previous studies. The aim of this master's thesis is to fill this gap by finding out if and to what extent children with congenital heart disease and very preterm children differ from each other and from a third group of healthy, full-term born children. The executive functions were measured with commonly applied cognitive tests and the volumes of the subcortical structures were evaluated through magnetic resonance imaging.

The following sections introduce the most important terms and concepts and review existing literature concerning executive functions in general and in preterm children and children with congenital heart disease. In addition, the hypotheses and research questions will be presented.

1.1 Executive Functions

Executive functions (EF) are higher cognitive processes which are required for volitional, purposeful actions. These interrelated processes regulate the basic psychological functions in a goal-directed way (Jäncke, 2017) and are particularly used in situations which cannot be mastered with experience or routine (Drechsler, 2007). Whenever the neutral preset of the organism, the "default mode", as it is called by Mesulam (2002), has to be deviated, EF are used – for example, when unexpected events occur, in new situations, when humans are setting goals or planning over several steps (Mesulam, 2002).

EF include different abilities such as working memory, cognitive flexibility, inhibition, visual-spatial planning, problem solving, reasoning and verbal fluency (Anderson, 2002). They have been shown to be essential for physical and psychological health, academic success and cognitive, social and psychological development (Diamond, 2014). Evolving during childhood and adolescence, EF can be assessed as early as 6-8 years and thereafter with increasing levels of complexity. Therefore they are crucial for interacting with others in social situations, emotional control and daily behavior of a child (Anderson, 2002).

For methodological reasons inherent in this thesis (as discussed in chapter 2), the focus is on the following three EF: working memory, cognitive flexibility and visual-spatial planning.

1.1.1. Working Memory

In almost all our daily activities, we must keep relevant information of events, which are no longer present but lie in the past, in mind. For example, when reading the end of a sentence, we must remember its beginning to be able to understand its content. Projects can only be put into action if these plans are still in mind. Diamond (2014) defines the prerequisite for this ability as working memory. Working memory does not involve simply holding relevant information in mind but holding it and being able to manipulate it. In contrast to short-term memory, WM enables us to organize and process the stored content and therefore is fundamental to making sense of everything that happens in life. Working memory can be divided into two types based on its content: verbal working memory and nonverbal (visual-spatial) working memory. (Diamond, 2014).

1.1.2. Cognitive Flexibility

Another fundamental EF which develops later than working memory is called cognitive flexibility. As Diamond (2014) explains, cognitive flexibility involves several aspects such as changing perspectives in the room (e.g., looking from a different direction) or taking perspectives of another person. For this process we need the ability to inhibit the active perspective and prioritize a new perspective which is different from the first one. For example, when we have actually planned to do A, but then suddenly the opportunity appears to do B, we need the flexibility to benefit from the advantages of this possibility (Diamond, 2014). Anderson (2002) also describes the ability to shift between response sets, to learn from mistakes and to divide attention as cognitive flexibility: “Inflexible individuals are generally considered rigid and ritualistic, struggling when activities or procedures are changed and failing to adapt to new demands” (Anderson, 2002, p. 74). Accordingly, individuals with deficits in this domain repeatedly make the same mistakes or repetitively break the same rules.

1.1.3. Visual-Spatial Planning

The third EF considered in this work is part of the goal setting domain. Anderson (2002) describes the domain as the ability to plan actions in an efficient strategic way based on the development of new initiatives and concepts. Individuals with deficits in this domain show several impairments in planning, organization and developing efficient strategies. These deficits result in a poor problem-solving ability – an ability that people need in nearly daily behavior. Especially during late childhood, goal setting skills are crucial because they are necessary for independent thinking and self-management (Burnett, Scratch, & Anderson, 2013).

1.2 Brain Structures

Performing executive tasks needs a neural basis. In order to have a better understanding of brain regions, which are of high relevance in relation to EF, this subchapter first gives a short introduction to the brain anatomy:

Every structure lying under the cortex (the outermost layer of the brain) is called a subcortical structure. The tissue of the brain can be divided into two types: grey matter (GM) and white matter (WM). Chambers (so-called ventricles), where no GM or WM is present, are filled with cerebrospinal fluid. The GM is formed by the cell bodies of neurons and dendrites, whereas the WM contains the connections between different neurons, so-called axons and glial cells (Jäncke, 2017).

Another, topological classification of the cortical brain distinguishes between different areas, so-called lobes. There is a frontal, parietal, occipital and temporal lobe (Jäncke, 2017), as illustrated in Figure 2.

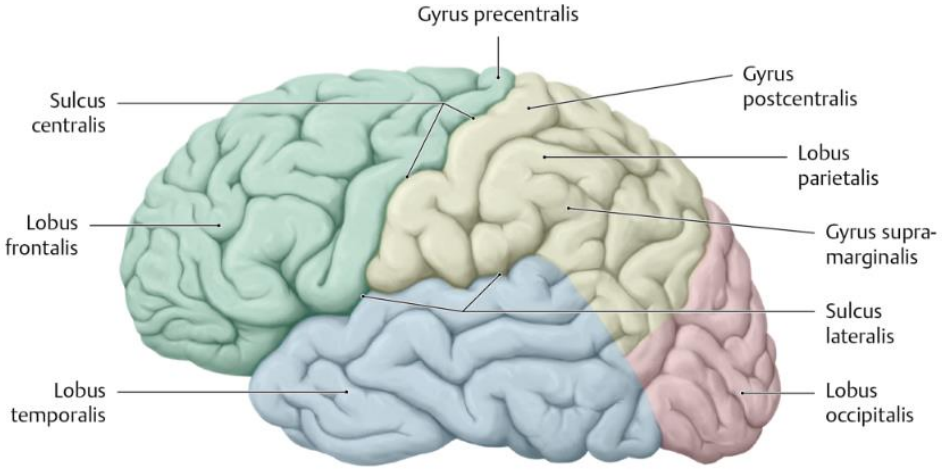

Figure 2: Brain lobes of the cortical brain illustrated with different colors (Schünke et al., 2009)

1.2.1 Relevant Brain Regions for EF

There are numerous studies showing the relevance of the prefrontal cortex for mediating EF in healthy individuals (Baker et al., 1996; Grattan & Eslinger, 1991; Morris, Ahmed, Syed, & Toone, 1993; Rezai et al., 1993; Stuss & Benson, 1984; Yuan & Raz, 2014). Since the prefrontal cortex is closely connected to many other brain regions, resulting in a network, it would be too simplistic to assume that the prefrontal cortex is the only region underlying EF. Rather, other regions in addition to this frontal region, namely the parietal, occipital, temporal and subcortical areas, are relevant for the execution of an executive task (Stuss & Benson, 1984).

The important role of particularly the *subcortical* brain regions in association with EF has been demonstrated through several studies, which examined children with congenital heart disease (Latal et al., 2016; von Rhein et al., 2013) and premature children (Allin et al., 2001; Nosarti et al., 2008; Taylor et al., 2011). Two of the next subchapters (1.4.2 and 1.5.2) describe in detail, which of the subcortical brain regions could be significant for performing executive tasks, especially in children with congenital heart disease and very preterm children. But first, a widely used method with which the structure of brains can appropriately be studied will be introduced.

1.3 Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) is a noninvasive tool to study the internal anatomy of living individuals (Storey, 2006). The aim of a structural MRI scan of the human brain is to visualize

and depict brain anatomical structures and make them available for further analysis. The basis for MRI is the spin of the hydrogen nucleus in living bodies. When hydrogen atoms are brought into a strong magnetic field, the spins of the hydrogen nuclei align along the magnetic field lines. The spins are then in a stable state. If this stability is disturbed by a high-frequency pulse, the spins tip over. The energy released by the spins when they return to their original position is measured by a radiofrequency coil and can be reconstructed into an image by connected computers. Depending on the frequency and phase of the measured signal, it is then possible to determine the position in the brain from which the signal comes, and the strength of the signal depends on the tissue type. The signal strength depends on two relaxation processes which describe the recovery process after the spins are disturbed by a radiofrequency pulse: T1 relaxation (longitudinal relaxation) and T2 relaxation (transverse relaxation). The measurement sequence based on this T1 relaxation is called T1-weighted imaging, while the measurement sequence sensitive to T2 relaxation is called T2-weighted imaging (Jäncke, 2005). For this master's thesis, the T1-weighted images are of essential importance.

So far, no negative effects of strong magnetic fields on the human body are known, therefore MRI is considered a safe imaging method (Storey, 2006). Nevertheless, it should be noted that there are some risks due to the strong magnetic field. The magnetic field can exert very strong forces on ferro-magnetic objects, which can lead to move them with high accelerations. This could lead to serious accidents. It is therefore important to ensure that no ferro-magnetic objects are brought into the room where MRI is used. In particular, persons who are scanned with the MRI must first remove all metallic objects they are carrying on their bodies. Persons with cochlear implants, pacemakers or other non-MR compatible implants are therefore excluded from the MRI examination (Jäncke, 2005).

1.4 Congenital Heart Disease

A congenital heart disease (CHD) is defined as a structural abnormality of the heart that exists at birth and is associated with functional impairment (Casey, 2016). CHD is the most commonly occurring congenital abnormality (Hoffman & Kaplan, 2002) and affects about 10 to 12 per 1000 live births (Hoffman, 2013). There are many different forms of CHDs. Depending on the severity, which ranges from minor defects to very complex abnormalities, the clinical presentation of CHD is different (Casey, 2016).

About half of all patients require immediate surgery after birth in order to survive. Great improvements in neonatal, perioperative care and surgical techniques resulted in more and more children with CHD surviving today. The survival rate has therefore risen to 80-90% even for children with very complex forms of CHD resulting in an increasing number of adolescents and adults living with CHD (Wernovsky, 2008). However, affected people are at high risk for

neurodevelopmental impairments in various domains (Calderon & Bellinger, 2015; Cassidy et al., 2015; Marino et al., 2012). The next subchapter will give an overview about the current state of the art regarding these impairments and in particular the impairments of EF.

1.4.1 EF in Children with CHD

In 2003, Bellinger and his team showed that children with CHD aged 8 years experience difficulties in neuropsychological tests. Although there was no control group in this project, the overall neuropsychological test performance was significantly below the expected performance in the general population. In particular, they had problems in alternating between tasks and they made more perseverative errors. This suggests that these children have an impaired cognitive flexibility (Bellinger et al., 2003). This study was the first to report EF deficits in school-aged children with CHD. The following studies show that EF remain impaired up to the higher adolescence age:

Bellinger and colleagues (2011) were able to show impairments in EF in the same group of children, now at an age of 16 years. They tested EF with the D-KEFS (Delis, Kaplan, & Kramer, 2001), a widely used battery for testing EF and derived an executive function summary score by averaging the standard scores of the subtests. The mean score was significantly lower for children with CHD than the expected value of 10 but as the standard deviations were larger than those expected in the general population, they suggest marked variability among children with CHD in their outcomes (Bellinger et al., 2011).

Later, Schaefer et al. (2013) wanted to determine neurodevelopment, psychological adjustment and health-related quality of life in adolescents after bypass surgery for CHD. They recruited adolescents with CHD aged between 11 and 16 years and compared them to a control group consisting of healthy adolescents aged between 9 and 16 years. In addition to the Wechsler Intelligence Scale for Children (WISC-IV) assessing verbal comprehension, perceptual reasoning, working memory and processing speed (Petermann & Petermann, 2006), they further tested the EF with the Rey-Osterrieth Complex Figure Test (ROCFT) (Rey, 1941). In the ROCFT, the subject is required to copy a complex geometric figure and then reproduce the figure from memory 15 minutes later. Results showed poorer neurodevelopmental outcomes on all the tests for the group with CHD than the control group (Schaefer et al., 2013).

The suggestion that children with CHD are at high risk for developing impairments in EF was further strengthened through work by Cassidy et al. (2015): The team examined study participants aged between 10 and 19 years. The aim of the study was to compare EF outcome in four different groups: three groups with different kinds of CHD and one healthy control group. Among other standardized methods, the D-KEFS (Delis et al., 2001) was used. Subtests assessing verbal generativity and switching (Verbal Fluency Test), visual-spatial generativity and

switching (Design Fluency Test), cognitive flexibility and problem-solving (Sorting Test), verbal concept formation and hypothesis-testing (Word Context Test) and visual-spatial planning (Tower Test) were performed. The results demonstrated that at least one group affected with CHD scored significantly worse than the controls in all subtests of D-KEFS, except in one variable (Move-Accuracy Ratio) out of three variables of the tower test. Furthermore, in another variable (Time per Move Ratio) of the tower test, all the CHD groups achieved lower values than the control group, indicating that individuals with CHD are less efficient in completing the task than the healthy study participants. Cassidy et al. (2015) summarize that the proportion of participants performing at least 1.5 standard deviations below the population mean on at least one D-KEFS subtest was almost twice as high in the CHD group (75-81%) compared to the proportion in the healthy control group (43%).

In summary, these findings indicate that CHD poses a risk for developing deficits in higher cognitive functions, i.e. EF.

1.4.2 Brain Volumes in Children with CHD

To find out which neuronal correlates underlie these impairments in EF, some studies in the last few years investigated how CHD and altered brain development are related. One of the most common abnormalities in the brains of children with CHD seems to be a volume reduction in certain areas of the brain (Latal et al., 2016; von Rhein et al., 2013; Watanabe, Matsui, Matsuzawa, Tanaka, & Noguchi, 2009).

Already in very young infants it was shown that CHD is associated with a smaller brain volume: Watanabe and colleagues have shown that children aged 15 months have reduced grey matter volumes (Watanabe et al., 2009). They thus laid the foundation stone for further studies which investigated the relationship between CHD and brain volume.

As von Rhein and colleagues demonstrated in 2013, children suffering from CHD still show these reduced brain volumes compared to a healthy control group at the age of 11 to 16 years (von Rhein et al., 2013). In their study, however, the researchers not only found reduced grey matter volume in cortical and subcortical regions, but also a smaller total white matter volume and a smaller total brain volume in children with CHD compared to healthy children of the same age. The reported reduced volumes in different subcortical regions included the cerebellum, thalami, basal ganglia and hippocampi. However, after correcting for total brain volume, the group differences in regional volumes mostly disappeared.

In addition to the reported differences in brain volume between children with CHD and heathy controls, these authors were also able to show an association between brain volume and functional outcome: Specifically, they found a positive correlation between total brain

volume and performance in working memory. This correlation was not present in the control group (von Rhein et al., 2013).

The results for reduced hippocampal volume in children with CHD were later replicated in a work by Latal et al. (2016). This study examined CHD patients aged 11 to 16 years. Compared to a healthy control group, the authors found, as already indicated, reduced volumes in both the left and right hippocampus. Correcting for total brain volume, there was no significant difference in hippocampal volume between CHD patients and healthy controls. Latal and her team also found a relationship between the reduced hippocampal volumes and cognitive outcome. Specifically, hippocampal volumes correlated positively with working memory performance, assessed by the WISC-IV, but only in the children with CHD and not in the control group (Latal et al., 2016).

The conclusion out of these presented studies is that certain brain regions, and particularly subcortical structures such as the hippocampus, are affected in children with CHD and that these neurological findings correlate with cognitive outcome, and in particular with functional deficits.

1.5 Very Preterm Birth

A human pregnancy usually lasts approximately 40 gestational weeks. However, sometimes it happens that birth occurs before these 40 weeks have been completed. If the birth takes place before the 37th week of pregnancy, it is called a preterm birth. A preterm birth can be further divided into moderately (32 – 36 weeks), very (28-31 weeks) and extremely (≤ 27 weeks) preterm birth (Johansson & Cnattigius, 2010).

In Switzerland, 7.5% of all births are preterm (Bundesamt für Statistik, 2010) and about 800 children are born very preterm every year (Bundesamt für Statistik, 2015). As a consequence of the improvements of medical care, more and more very preterm babies survive without any major impairments (Rüegger, Hegglin, Adams, & Bucher, 2012). But increasing number of studies suggest that these children are at high risk for mild forms of cognitive, motor and social problems (Aarnoudse-Moens et al., 2009). The next subchapter will present the existing literature about this topic in more detail.

1.5.1 EF in Children Born Very Preterm

40-50% of very preterm children develop cognitive and behavioral deficits, which can significantly impair academic success and quality of life of these children as they grow older (Larroque et al., 2008; Moore, Hennessy, Johnson, & Draper, 2012; Schlapbach et al., 2012).

Anderson & Doyle (2004) showed that children born very preterm not only exhibit academic and psychosocial impairments, as reported by Grunau, Whitfield, & Fay (2004), but also have deficits in their EF compared to term-born children (Anderson & Doyle, 2004) and there are several other studies reporting cognitive deficits especially in EF. The suggestion that very preterm children have moderate to severe impairments in EF abilities and that these deficits persist into young adulthood was shown through a meta-analysis of Aarnoudse-Moens et al. (2009).

An early study by Luciana and her team (1999) showed that 7-to-9-year-old children born preterm have impairments in certain executive functions compared to a term-born control group. Among other things, the researchers assessed spatial working memory and visual-spatial planning. The results showed that children born preterm performed worse in both dimensions than children in the control group but this difference only became apparent with increased task difficulty (Luciana et al., 1999). However, one limitation of this study is that cognition has only been assessed with visuo-spatial but not verbal tests.

In a large study, Aarnoudse-Moens and colleagues (2011) assessed the EF in very preterm children aged between 4 and 12 years. Cognitive flexibility was tested with a stimulus-response compatibility task where children had to response to stimuli with different colors calling for a different response set. Furthermore, the authors assessed visual-spatial working memory using a computer-based task similar to the Corsi Block Tapping Task and verbal working memory assessed through the Digit Span Test (Wechsler, 1949). A touch-screen-adapted version of the Tower Test was used to asses visual-spatial planning. The team reported poorer scores for very preterm children in variables of the visual-spatial and verbal working memory and in visual-spatial planning compared to term-born controls. No differences between very preterm children and the control group were revealed in cognitive flexibility (Aarnoudse-Moens et al., 2011).

Anderson & Doyle (2004) comprehensively tested a group of 8-year-old children born very preterm for their EF in a large study. Besides reasoning and conceptualization, working memory and planning ability were assessed. Verbal working memory was tested through the Digit Span Test (Wechsler, 1949) whereas the Tower of London, which is similar to the Tower Test (Delis et al., 2001), assessed visual-spatial planning. The results clearly show that children born very preterm exhibited impairments in all the assessed EF compared to a term-born control group (Anderson & Doyle, 2004).

Also Ritter, Nelle, Perrig, Steinlin, & Everts (2013) reported, that children born very preterm and currently aged 8 to 10 years achieve worse results in tests assessing inhibition (Color-Word Interference, D-KEFS (Delis et al., 2001)), working memory (Digit Span Task, WISC-IV (Petermann & Petermann, 2006)) and shifting (Trail Making Test, D-KEFS (Delis et

al., 2001)) compared to a term-born control group. Nevertheless, all the kids performed above the threshold of clinical impairment (Ritter et al., 2013).

Indications for deficits in EF persisting into adolescence were given by a work of Saavalainen et al. (2007). They focused on working memory by assessing verbal and visual-spatial working memory. Children aged 16 years were tested and compared with a group of term-born children of the same age. Significant differences between the two groups were reported for the spatial span backward, where participants had to touch a series of blocks in the reverse order than presented through the examinee. However, preterm born children did not differ significantly from the term-born children in verbal working memory (Saavalainen et al., 2007).

These findings could be replicated through work by Luu, Ment, Allan, Schneider, & Vohr (2011) who also tested 16-year-old children. With subtests of the D-KEFS (Delis et al., 2001), they assessed verbal fluency, cognitive flexibility and visual-spatial planning. Visual working memory was tested with the same test as that used by Saavalainen et al. (2007). The authors reported lower scores in all the tested domains for children born very preterm compared to a term-born control group. Significant impairment (< 2 SD) was found in 6% to 18% of preterm adolescents compared with only 1% to 3% of term-born children. The results were also confirmed by the parents as they reported more difficulties in initiation of activities or generation of new ideas and with working memory in their children on a questionnaire. This indicates that problems in EF are also manifested in daily behavior at home (Luu et al., 2011).

In summary, the reported studies show a consistent picture of poorer EF performance in children born very preterm compared to term-born children indicating a risk for developing deficits in these cognitive functions for these children.

1.5.2 Brain Volumes in Children Born Very Preterm

It is also important to explore the underlying neuronal correlates of impaired EF in children born very preterm. Several studies suggest that one reason for impaired EF in children born very preterm could be reduced brain volumes (de Kieviet et al., 2012).

In their meta-analysis, de Kieviet et al. (2012) summarized that both global and regional volume differences between preterm children and term-born children have been found so far: Preterm-born children have smaller brain volumes than term-born children. Regionally, the hippocampus, the cerebellum and the corpus callosum are affected, but the findings for the volume reduction of the corpus callosum were heterogeneous and should therefore be interpreted with caution (de Kieviet et al., 2012).

For example, Nosarti et al. (2002) presented decreased whole brain volumes in 14-to-15-aged preterm-born children compared to full-term controls. They further reported reduced cortical grey matter and enlarged lateral ventricles in preterm-born children after controlling for total brain volume compared to controls (Nosarti et al., 2002).

Taylor et al. (2011) could replicate these findings in their study with adolescents aged between 14 and 19 years. Very preterm-born adolescents had smaller total brain volumes as well as decreased WM and GM volumes compared to a group of age-matched term-born children. They could also find larger ventricles in adolescents born very preterm (Taylor et al., 2011).

Smaller cerebella in very preterm-born adolescents aged between 14 and 15 years were first reported by Allin et al. (2001). In their study, the very preterm-born group was compared to a control group consisting of term-born adolescents of the same age. The significantly reduced cerebellar volume in very preterm-born cases was still present after controlling for total brain volume (Allin et al., 2001). Also Taylor and colleagues (2011) reported smaller cerebella in their very preterm-born group. They found reduced volumes for cerebellar WM and cerebellar GM respectively (Taylor et al., 2011).

In addition to reduced cerebellar white matter volumes in 15-year-old preterm-born children, Martinussen et al. (2009) further found reduced volumes in the thalamus compared to a term-born control group. These results persisted after correcting for total brain volume.

Nosarti et al. (2008) conducted a study with 14-to-15-year-old participants. The team showed that very preterm-born adolescents have smaller thalamic volumes compared to an age-matched control group. Further, they reported reduced subcortical volumes in the basal ganglia, more precisely in the putamen and caudate nucleus (Nosarti et al., 2008).

Finally, Nosarti and her team additionally showed that there are reduced hippocampal volumes in children born very preterm compared to term-born children and these findings persisted after controlling for total brain volume (Nosarti et al., 2002).

Structural alterations such as reduced GM and WM volume have been shown to account for 29% of the variance in executive function abilities (verbal and non-verbal memory, among other things) in adolescents born preterm (Nosarti et al., 2008). Also Taylor and his team reported robust associations between neuropsychological outcomes (processing speed, working memory, set shifting and visual attention) and brain volume reductions in very preterm-born adolescents (Taylor et al., 2011).

Taken together, children born very preterm seem to have smaller volumes in certain brain regions, particularly in the subcortical brain structures such as the cerebellum, the thalamus or the hippocampus. Furthermore, these brain volumes were shown to correlate with cognitive outcome, and in particular with deficits in EF.

1.6 Research Questions and Hypothesis

The current findings about EF and brain volumes in children with CHD and children born very preterm presented in the previous subchapters show a very similar picture – both, in EF impairments and reduced brain volumes. However, no study has yet been conducted to compare the two clinical groups directly.

Therefore, the aim of this work is to fill this gap and to compare these groups with each other. In doing so, possible similarities and differences between the two groups may be uncovered. In addition, the results will be compared with the values of a healthy term-born group acting as a control group. The following part presents the hypotheses, which are to be tested by this master's thesis:

- Hypothesis 1: Children with congenital heart disease and very preterm children have similar deficits in their executive functions compared with controls.
- Hypothesis 2: The volumes of cerebellum, thalamus, hippocampus, basal ganglia and whole brain are similarly reduced in children with congenital heart disease and very preterm children compared to controls.
- Hypothesis 3: There is a correlation between brain volumes and executive functions.

2. Methods

The data basis for this master's thesis is provided by two large research projects that are currently being carried out at the University Children's Hospital Zurich. This section first presents these two projects, before the methodological approach and the analysis methods are described in more detail.

2.1 Brain network function in school-age children with congenital heart disease and its relation to higher order cognitive functions (BF_CHD)

The BF_CHD study has the aim to determine the extent and severity of EF deficits and potential neuronal correlates in school-aged children born with CHD. The results are compared to a healthy control group. The study intends to find answers to the questions of whether children with CHD, aged between 9 and 11 years, have a delayed brain maturation (assessed with MR imaging or sleep electroencephalography (EEG)) compared to healthy controls and whether EF deficits are correlated with potential markers of such a maturational delay.

2.1.1 Recruitment and Inclusion Criteria (BF_CHD)

All the participants in the CHD group are recruited while they are at the Child Development Center at the University Children's Hospital Zurich for a follow-up visit as a part of the study "Long-term development and quality of life after cardiopulmonary bypass surgery" (KEK-ZH-Nr. 2014-0071). Children participating in the CHD group should meet the following inclusion criteria:

- Born with a congenital heart disease
- Underwent cardiopulmonary bypass surgery during first three months of life
- No genetic syndrome detected
- Gestational age > 37 weeks of gestation
- Aged 9;0 to 11;11

For the control group, friends of the children with CHD are recruited. Parents of the children in the CHD group are asked whether their child has a friend of the same age who would like to participate too. The inclusion criteria for the children in this group are that they are aged between 9 and 11 years and healthy without any congenital heart defect. Furthermore, the children should be born at term (> 37 weeks of gestation).

2.1.2 Procedure (BF_CHD)

After the parents agree to the participation of their child in the study, children come to the Child Development Center at the University Children's Hospital Zurich. After explaining the procedure and discussing the formalities, the neurodevelopmental assessment (2.5 hours) takes place in the afternoon. The children then stay for one night in the Hospital for a sleep EEG recording, which isn't part of this work and, thus, will not be explained in more detail. In the morning, the MRI is performed (45 minutes).

2.2 Long-term neuroprotective effect of erythropoietin (Epo) on executive functions in very preterm children (EpoKids)

This research project is a follow-up of a double-blind, placebo-controlled study entitled "Does Erythropoietin (Epo) improve outcome in very preterm children" (NCT00413946, KEK StV-36/04), which was conducted at the University Hospital Zurich between 2005 and 2012. Half of the very preterm infants included in the study were given erythropoietin (Epo), a potentially neuroprotective agent, while the other half received a placebo. Epo was shown to reduce the risk for neonatal brain injury (Leuchter et al., 2014).

The project 'EpoKids' now investigates the long-term effects of Epo on the development of EF in children aged between 7 and 13 years. The main aim is to determine whether Epo has beneficial effects on these functions and to what extent Epo treatment may close the neurodevelopmental gap between very preterm children and typically-developing term-born peers. At the same time, the potential protective effect of early Epo treatment on neuronal networks is to be studied by various structural and functional MR images (Wehrle et al., 2018).

2.2.1 Recruitment and Inclusion Criteria (EpoKids)

The very preterm children are recruited from the original study cohort. The inclusion criteria are the participation in the study "Does Erythropoietin (Epo) improve outcome in very preterm children" (NCT00413946, KEK StV-36/04) and an age between 7 and 13 years. Chronic neurological diseases not caused by preterm birth are a criterion for exclusion.

Participants of the term-born control group are recruited through the families of the very preterm children by asking the families whether a friend of the same age as the participating very preterm child is interested in participating too. In addition, participants are recruited through flyers at the Children's University Zurich and the study is also promoted on the homepage of the University Children's Hospital Zurich. Inclusion criteria for control participants are term-birth (> 37. gestation week), an age between 7 and 13 years, no neonatal complications and no current or past developmental pediatric or neurological disease.

2.2.2 Procedure (EpoKids)

Children come to the University Children's Hospital for one day after the parents agreed to their participation in the study. In the morning, the procedure is explained, and the written informed consent of the parents is obtained. Then, the first part of the neurodevelopmental assessment takes place (2.5 hours). After lunch, the second part (1.5 hours) is conducted before the MRI (45 minutes) is performed.

2.3 Selection of Participants for this Master's Thesis

All the participants included in this master's thesis participated in one out of the two described research projects at the University Children's Hospital Zurich. As the participants in the BF_CHD study are aged between 9 and 11 years, only kids in this age range were selected from the EpoKids study. The goal was to include 15 children per group (CHD, preterm and control) resulting in a total of 45 participants.

2.3.1 Children with CHD

Since the BF_CHD project does not include many children (due to e.g., hesitation to stay over-night for sleep EEG assessment or exclusion from MR assessment due to medical implants) all the participants with CHD who had MRI were included in this work, regardless of whether they had undergone all EF tests or not.

2.3.2 Preterm Children

The study participants were selected from the EpoKids study list of participants, sorted by registration for the study, according to the following criteria:

- Age between 9;0 and 11;11 years
- The MRI was conducted
- All the tests of the EF, which are part of this work, were carried out

If one of the criteria was not fulfilled, the next participant in the list was checked for the criteria.

2.3.3 Control Group

All the healthy children with MRI of the BF_CHD study were included in the control group which was further supplemented with term-born participants of the EpoKids study who met the criteria described in subsection 2.3.2.

2.4 Assessment of the EF

The two studies have a very similar testing protocol. For this work, those tests of EF were included which overlap between the two projects, i.e. are carried out in both projects. This resulted in a total of six tests which measure the three EF, namely: working memory, cognitive flexibility and visual-spatial planning.

EF were assessed using standardized neuropsychological tasks. All tasks have previously been used in typically-developing or very preterm populations of a similar age and are frequently used in clinical routine as well as for research purposes. The following subsections give an overview of all applied tests and describes them in detail.

2.4.1 Working Memory

Working memory was tested in both domains (as described in subchapter 1.1.1) – the non-verbal (visual-spatial) working memory and the verbal working memory.

The Testbatterie zur Aufmerksamkeitsprüfung (TAP) is a well validated set of tests to selectively assess specific aspects of attentional processes (Zimmermann & Finn, 1993). The subtest *Working Memory* assesses non-verbal working memory by a 2-back task. In this numeric task, single numbers from 1 to 9 appear on a computer screen one after the other. The test person's task is to press a button as fast as possible every time a number appears, that is identical to the number before the last one. Response time, correct responses, errors and omissions are measured. The most important parameters are the omissions as they indicate a lack of control. Furthermore, the number of errors are of high importance as they could be an indication for inattention (Zimmermann & Finn, 1993). Therefore, these two variables were included in this work with higher scores indicating poorer performance in the task. As there are no norms available for children younger than 11 years, raw scores were used for further analyses.

Another test for assessing non-verbal working memory is the Corsi Block Tapping Task (Kessels et al., 2000). It tests the visual-spatial working memory in a forward and backward condition. In front of the test person lies a board with nine black blocks (see Figure 3). The test leader touches these blocks in a certain order with a pen, whereupon the test person is required to touch the blocks in the same order with his/her finger. The number of typed blocks increases with correct reproduction. In the second condition, the test person is required to touch the blocks in reverse order than the order presented by the test leader. Outcome

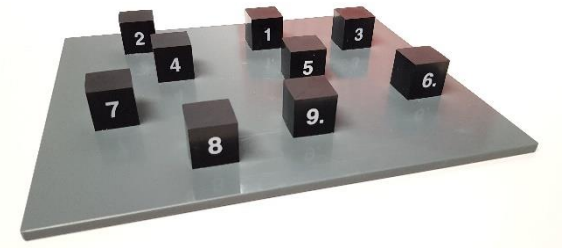

Figure 3: Illustraion of the Corsi Block Tapping Task from the test leader's perspective (own illustration)

variables are provided for the highest span length and for the number of correctly reproduced sequences for both the forward and the backward condition, separately. Better performance (and therefore better visual-spatial working memory capacity) is indicated by higher scores. There are no norms available for the Corsi Block Tapping Task, so raw scores had to be used for further analyses.

The verbal working memory is assessed through the *Digit Span Test* from the German adaptation of the Wechsler Intelligence Scale for Children (WISC-IV) (Petermann & Petermann, 2006). In this subtest, a certain sequence of single numbers is presented verbally to the subject, who then must repeat these numbers in the same sequence. Again, the degree of difficulty increases with correct replies, as the sequence of numbers becomes longer. In the reverse condition, the test person must repeat the numbers in reverse order than the order presented by the test leader. The resulting outcome variable is the number of correctly replied sequences summed up for the two conditions. Higher scores indicate better performance and thus better verbal working memory capacity. Raw scores were converted into aged-matched norm values available for different age according to the test manual (Petermann & Petermann, 2006).

2.4.2 Cognitive Flexibility

Two tests assessing cognitive flexibility are overlapping in the two projects: the Regensburger Wortflüssigkeitstest (RWT) and the subtest *Flexibility* of the TAP.

The Regensburger Wortflüssigkeitstest (RWT) tests the cognitive flexibility in a verbal condition (Aschenbrenner, Tucha, & Lange, 2000). Participants are asked to generate as many words as possible within two minutes. Words from the category “Sports” and the category “Fruits” are to be given alternately, so the test person must switch between these categories. The test results in two variables representing the number of words named in one and in two minutes, respectively. The higher the number of words mentioned, the higher the performance, i.e. the test person is highly cognitive flexible. Raw scores were converted into aged-matched norm values available for different age according to the test manual (Aschenbrenner et al., 2000).

The subtest *Flexibility* of the TAP is a non-verbal assessment of the ability to rapidly shift attention between different sets of stimuli (Zimmermann & Finn, 1993). The test person sits in front of a computer, where a pair of shapes appears on the screen one after the other. A pair always contains one edged and one round shape. The subject has two buttons – one on the right and one on the left side. When the first pair appears, the test person must press the button as fast as possible on the side, on which the edged shape is shown on the screen. For the next pair, the subject must switch and press the button on the side where the round

shape appears, following pressing the button again on the side with the edged shape, etc. Instructions in German are shown in Figure 4. Median reaction time, correct responses and errors are the resulting outcome variables. The most important variables are the amount of false reactions (errors) and the median reaction time, with higher scores indicating poorer performance (Zimmermann & Finn, 1993). Therefore, these variables were considered for this work. As there are no norms available for the required age range, raw scores had to be used for the further analysis.

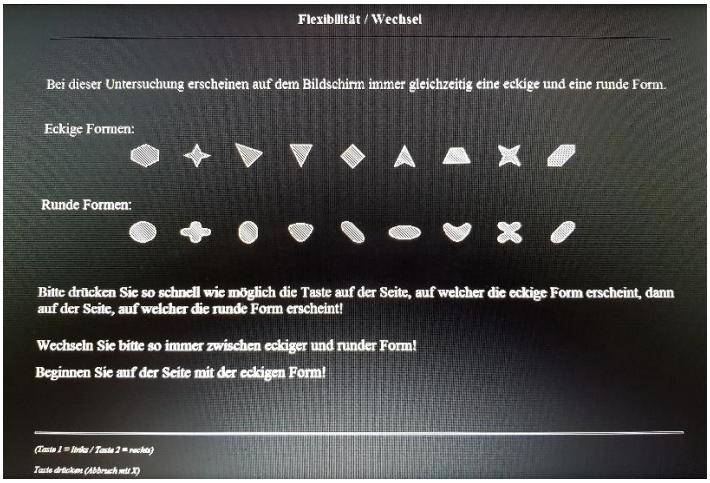

Figure 4: Illustration of the German instructions for the Flexibility subtest of TAP (Zimmermann & Finn, 1993)

2.4.3 Visual-Spatial Planning

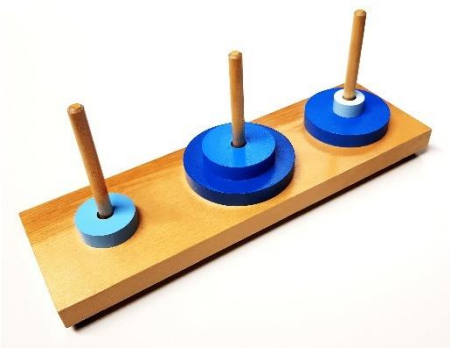

Figure 5: Photography of the test material used for the Tower Test (own illustration)

The Delis-Kaplan Executive Function System (D-KEFS) contains a set of key tasks to assess EF in a standardized manner (Delis et al., 2001). For assessing visual-spatial planning, the subtest *Tower Test* is used. In this task, the subject must build towers, consisting of up to five flat discs, lying on a board with three vertical pegs, according to a template. The person should do this with the minimum number of moves. There are two rules to follow: first, only one disc should be moved at a time and second, a large disc should never be placed on a smaller disc. The number of moves is counted and the time, the test person needs to build the tower, is measured. Rule breaks are also noted in the protocol. The fewer moves that are needed to build the tower, the greater the achievement score per administered item. The evaluation of the *Tower Test* leads to many variables. For this work, only the following variables were considered, corresponding to Cassidy et al., (2015):

- Total achievement score: the sum of the achievement scores across all items administered

- Time-Per-Move Ratio: indication of the average time the subject needs to make each of his or her moves. The ratio results from dividing the total of completion times by the total number of moves across all items administered.
- Move Accuracy Ratio: measure of the efficiency with which the examinee constructed the towers. This ratio results from dividing the total number of moves used by the subject by the number of minimal moves required across all items administered

All the raw scores of these variables were converted to scaled scores corrected for age. Higher scaled scores indicate better performance and thus better visual-spatial planning ability (Delis et al., 2001).

2.5 MRI Procedure

MRI images were acquired on a 3T GE whole-body system at the Center for MR Research at the University Children's Hospital Zurich (see Figure 6). The scanning protocol consisted of a combination of structural, functional and spectroscopy imaging sequences which are routinely used in clinical care and for research purposes. Children could hear an audiobook or radio while the scanning except for one sequence of about 6 minutes – the functional resting state sequence. A standardized safety screening questionnaire for the MRI measurement was filled out by the parents. Only if no concerns regarding the suitability of a child for the measurement from this questionnaire were presented, were the children scanned by the MRI and thus included in this work. Therefore, also Children with CHD carrying an implant were only scanned, when they were MR-save according to guidelines.

Figure 6: Image of the 3T GE whole body system at the Center of MR Research at the University Children's Hospital Zurich (own illustration)

To study the brain volumes, only the high resolution three-dimensional T1-weighted gradient echo images were used. Images were preprocessed by FreeSurfer image analysis

suite (http://surfer.nmr.mgh.harvard.edu/) doing cortical reconstruction and volumetric segmentation (Fischl, 2012). FreeSurfer is a freely available program with high test-retest reliability (Han et al., 2006) and has been validated through the manual gold standard method (Mayer et al., 2016). It was also shown to work appropriately for images of children brains (Ghosh et al., 2010).

2.6 Statistical Analyses

All the statistical analyses were done using SPSS (IBM SPSS Statistics 25). After testing for normal distribution with the Shapiro-Wilk test, homogeneity of variance was tested for the normally distributed variables. To compare the three groups (CHD, preterm, controls), univariate analyses of variance (ANOVA) were performed if the variables were normally distributed and their variances homogeneous. For variables which were non-normally distributed, or variance homogeneity was not given, the Kruskal-Wallis test was performed to compare groups in these dimensions. Appropriate post-hoc tests were applied to identify specific group differences. Effect sizes for the group comparisons were calculated with the Psychometrica calculator (Lenhard & Lenhard, 2016).

To assess whether performance differences between groups were connected to differences in brain volumes, correlations were analyzed with the Pearson's correlation coefficient (normally distributed variables) or the Spearman's correlation coefficient (non-normally distributed variables).

3. Results

The first step was to check the assumptions in order to decide which statistical methods are appropriate. Shapiro-Wilk tests were significant for all but three variables of the EF tests in at least one group per variable. This indicates non-normal distribution in these groups in the respective data. The MRI data was normally distributed for all three groups apart from one variable which was non-normally distributed in the group of very preterm children (see Table 1 and Table A2 in the appendix). Levene's test wasn't significant for any but one of the normally distributed variables. Therefore, for all but one normal-distributed variables, variances were equal in the three groups (see Table A3 in the appendix).

3.1 Participants

A total of 45 children were included in this work: 12 children with CHD, 17 very preterm children and 16 healthy term-born control children. Age was significantly different between the groups $H(2) = 10.64$, $p < .05$, with a median age of 10.86 (10.40-11.42) years for children with CHD, 11.17 (9.92-11.75) years for very preterm children and 10.29 (9.00-11.25) years for the control group. Mann-Whitney tests were used to follow up this finding. Age was different between very preterm children and the control group, $U = 50.00$, $p = .002$, $d = 1.28$ indicating higher age for very preterm children. However, there was no difference between very preterm children and children with CHD ($U = 60.00$, $p = .10$, $d = 0.74$), or children with CHD and controls ($U = 64.50$, $p = .09$, $d = 0.58$) respectively.

3.2 Hypothesis 1 (EF Outcome)

Table 1 shows the group comparisons in all the variables of EF outcome. For time reasons the TAP wasn't assessed for one participant leading to missing values in all the TAP variables for this child. In addition, the Digit Span Test wasn't assessed in one child due to time pressure. Further, there are missing values for nine participants in all the Tower Test variables due to test leader errors which makes the evaluation of this test impossible.

Analysis of variance revealed a significant group difference in the Highest Backwards Span Length of the Corsi Block Tapping Task, $F(2, 44) = 1.95$, $p < .05$. An independent-samples t-test indicated that scores were significantly lower for children with CHD ($M = 5.42$, $SD = 1.51$) than for controls ($M = 6.50$, $SD = 1.26$), $t(26) = 2.07$, $p = .049$, $d = 0.79$. There were also significantly lower scores for very preterm children ($M = 5.24$, $SD = 1.44$) compared to controls, $t(31) = 2.68$, $p = .012$, $d = 0.93$. Children with CHD didn't differ from very preterm children in their Corsi Block Backwards Span, $t(27) = 0.16$, $p = .75$, $d = 0.06$ (Figure 7).

Table 1: Sample size, mean and standard deviation (or median and range for non-normally distributed variables), test statistics and p-value of all EF measures

		CHD		Preterm		Control		Test Statistics	*p*
		n	*M* (*SD*) / *Mdn* (range)	n	*M* (*SD*) / *Mdn* (range)	n	*M* (*SD*) / *Mdn* (range)		
Working Memory	Corsi Block Tapping Task								
	Number of Correct Sequences (Forwards)[a]	12	8.5 (5.0 – 11.0)	17	8.0 (6.0 – 12.0)	16	9.5 (6.0 – 11.0)	1.95	.38
	Highest Span Length (Forwards)[a]	12	6.0 (4.0 – 8.0)	17	6.0 (4.0 – 8.0)	16	6.0 (4.0 – 8.0)	0.44	.80
	Number of Correct Sequences (Backwards)[a]	12	8.0 (3.0 – 13.0)	17	8.0 (4.0 – 11.0)	16	9.5 (6.0 – 12.0)	5.15	.076
	Highest Span Length (Backwards)[b]	12	5.42 (1.51)	17	5.24 (1.44)	16	6.50 (1.26)	3.80	.030
	TAP Working Memory								
	Number of Errors[a]	12	2.5 (0.0 – 16.0)	17	2.0 (0.0 – 18.0)	15	2.0 (0.0 – 14.0)	0.42	.81
	Omissions[a]	12	4.5 (2.0 – 12.0)	17	5.0 (2.0 – 11.0)	15	4.0 (0.0 – 10.0)	1.71	.43
	Digit Span Test								
	Number of Correct Sequences[b]	12	9.58 (3.06)	17	8.94 (2.93)	15	9.60 (2.23)	0.29	.75
Cognitive Flexibility	TAP Flexibility								
	Number of Errors[a]	12	5.5 (1.0 – 19.0)	17	6.0 (0.0 – 22.0)	15	7.0 (0.0 – 18.0)	0.12	.94
	Reaction Time (ms)[a]	12	991.5 (810 – 1560)	17	997.0 (738 – 1346)	15	929.5 (639 – 1180)	2.53	.28
	RWT (Sports/Fruits)								
	Number of Words, 1st Minute (Percentile Rank)[a]	12	56.0 (4.0 – 98.0)	17	55.0 (0.0 – 98.0)	16	70.0 (0.0 – 98.0)	0.59	.74
	Number of Words 2nd Minute (Percentile Rank)[b]	12	52.58 (25.17)	17	51.35 (28.81)	16	52.38 (30.25)	0.01	.99
Visual-Spatial Plan-	Tower Test								
	Total Achievement Score[a]	9	11.0 (9.0 – 23.0)	15	11.0 (5.0 – 18.0)	12	11.0 (9.0 – 15.0)	0.12	.94
	Time-Per-Move Ratio[a]	9	12.0 (10.0 – 12.0)	15	11.0 (6.0 – 14.0)	12	12.0 (9.0 – 14.0)	2.94	.23
	Move Accuracy Ratio[a]	9	9.0 (1.0 – 11.0)	15	7.0 (4.0 – 11.0)	12	9.0 (3.0 – 13.0)	0.99	.61

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest

[a]analyzed with a Kruskal-Wallis test, leading to median (*Mdn*) and *H*-values for test statistics, [b]analyzed with an ANOVA, leading to mean (*M*) and standard deviation (*SD*) and *F*-values for test statistics

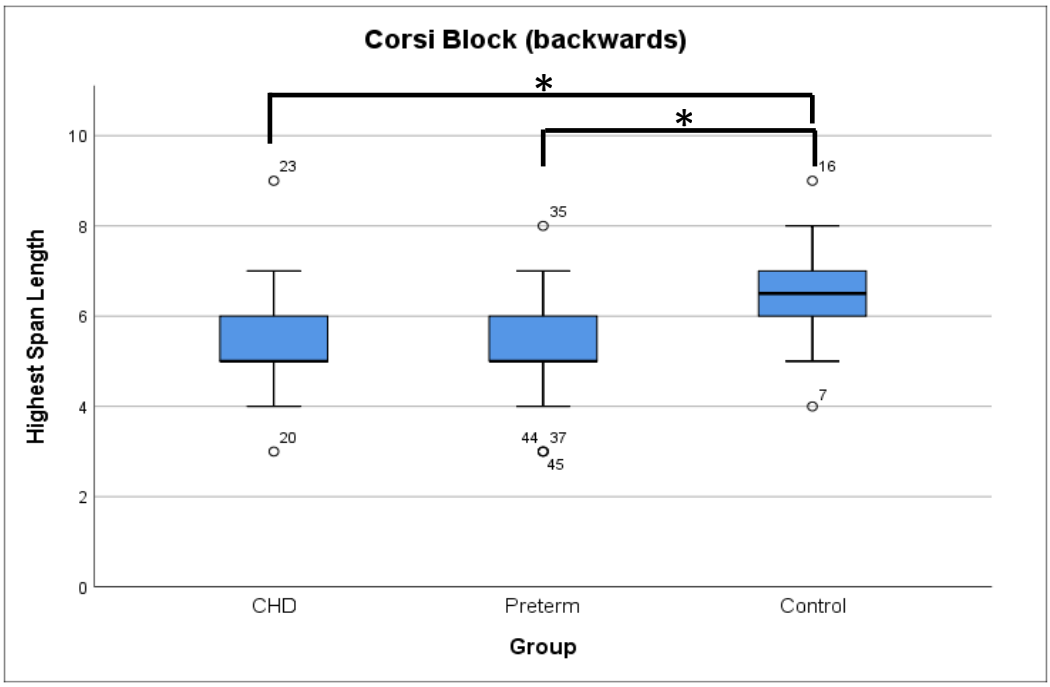

*Figure 7: Highest backwards span length in Corsi Block Tapping Task with * indicating significant differences between the corresponding groups on a significance level of .05*

None of the other EF variables differed significantly between the groups (Table 1). Figure 8 shows an example of a non-significant result indicating no differences between the groups in cognitive flexibility. However, the mean values show a tendency towards poorer performance in RWT both in children with CHD and very preterm children compared to the healthy term-born group. A tendency towards poorer EF in children with CHD and very preterm children can also be seen in nearly all the other EF variables (see Figure A 1 to Figure A 12 in the appendix).

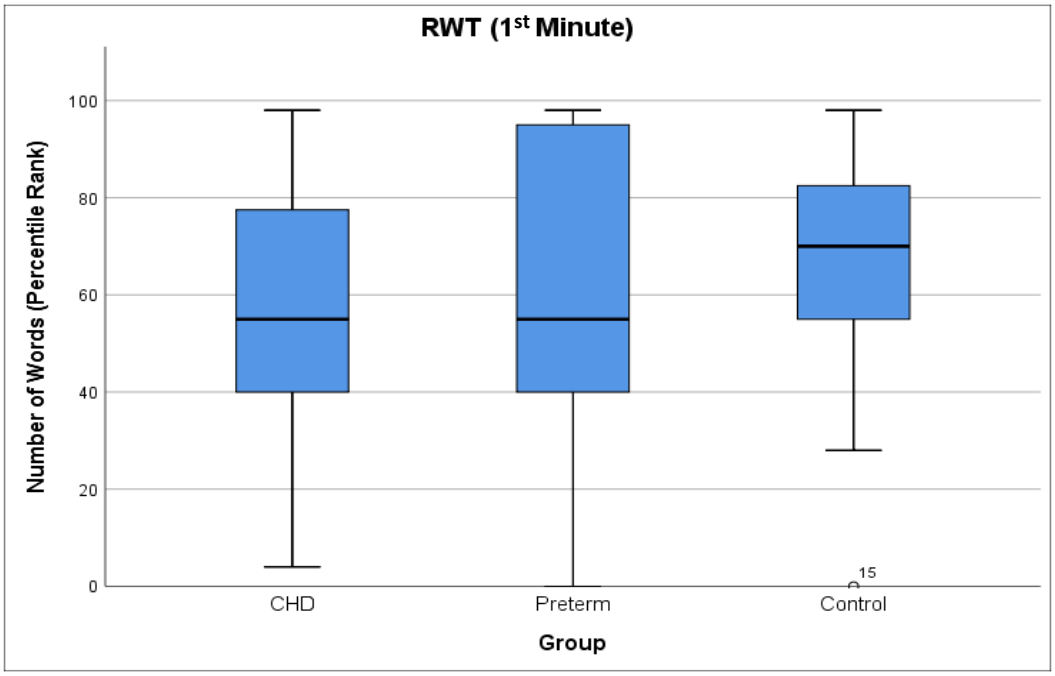

Figure 8: Number of Words in percentile rank of the Regensburger Wortflüssigkeitstest (RWT) for each group with no significant differences between the groups.

3.3 Hypothesis 2 (Brain Volumes)

Table 2 shows the results from group comparisons in all the variables relating to the subcortical brain volumes. Due to motion artefacts, the volumetric segmentation through FreeSurfer wasn't done appropriately, so one participant had to be excluded for further analyses. Analysis of variance showed a significant group difference in the volumes of left cerebellar WM, $F(2, 43) = 4.06$, $p < .05$. An independent-samples t-test indicated that volumes were significantly lower in children with CHD (M = 12'253 mm^3, SD = 1'923 mm^3) than in controls (M = 14'206 mm^3, SD = 2'053 mm^3), $t(26) = 2.56$, $p = .017$, $d = 0.98$. No significant differences were observed between very preterm children (M = 13'431 mm^3, SD = 1'378 mm^3) and children with CHD, $t(26) = -1.89$, $p = .070$, $d = -0.72$, or controls, $t(30) = 1.25$, $p = 0.22$, $d = 0.44$, respectively (Figure 9).

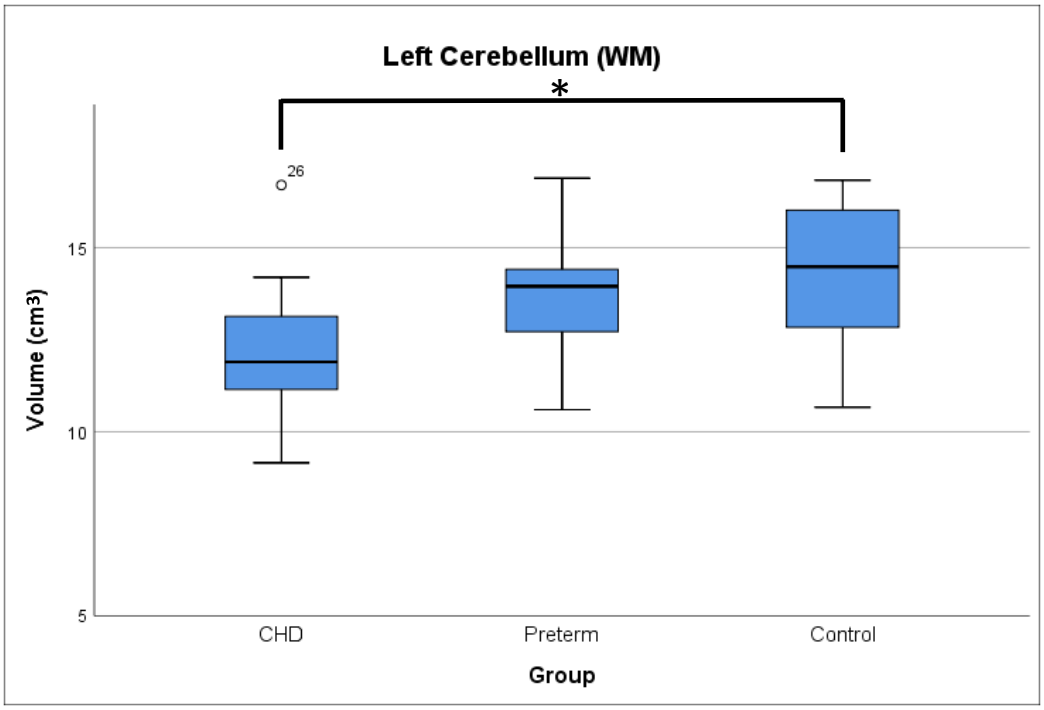

*Figure 9: Left cerebellar volumes in the white matter from each group with * indicating significant differences between the corresponding groups at a significance level of .05. Volumes are reported in cm^3.*

Table 2: Sample size, mean and standard deviation (or median and range for non-normally distributed variables), test statistics and p-value of all the subcortical brain volumes (in mm^3).

		CHD (*n* = 12) *M* (*SD*) / *Mdn* (range)	Preterm (*n* = 17) *M* (*SD*) / *Mdn* (range)	Control (*n* = 16) *M* (*SD*) / *Mdn* (range)	Test Statistics	*p*
Subcortical Brain Volumes	Cerebellum					
	WM Left[b]	12'253 (1'923)	13'431 (1'378)	14'206 (2'053)	4.06	.025
	WM Right[a]	12'447 (9'382 – 18'189)	13'758 (12'313 – 15'417)	14'344 (10'232 – 19'775)	4.87	.088
	GM Left[b]	49'015 (6'269)	49'787 (4'043)	50'937 (5'034)	0.51	.60
	GM Right[b]	50'967 (5'913)	49'408 (5'083)	50'613 (7'131)	0.26	.77
	Thalamus					
	Left[b]	6'341 (579)	6'681 (671)	6'712 (594)	1.45	.25
	Right[b]	6'351 (803)	6'503 (758)	7'017 (776)	2.97	.063
	Hippocampus					
	Left[b]	3'294 (391)	3'445 (394)	3'624 (389)	2.48	.096
	Right[b]	3'367 (496)	3'468 (420)	3'667 (302)	2.04	.14
	Basal Ganglia					
	Caudate Left[b]	3'590 (436)	3'875 (636)	4'114 (508)	3.21	.051
	Caudate Right[b]	3'811 (510)	4'104 (612)	4'348 (499)	3.33	.046
	Putamen Left[b]	6'388 (795)	6'163 (876)	6'406 (453)	0.54	.59
	Putamen Right[b]	6'284 (845)	5'902 (615)	6'228 (535)	1.45	.25
	Pallidum Left[b]	1'619 (208)	1'610 (202)	1'747 (212)	2.10	.14
	Pallidum Right[b]	1'586 (220)	1'566 (191)	1'710 (174)	2.54	.091
	GM					
	Total[b]	56'001 (5'791)	56'288 (5'446)	59'358 (4'359)	1.95	.16

WM: white matter, GM: grey matter, *n:* subsample size

[a]analyzed with a Kruskal-Wallis test, leading to median (*Mdn*) and *H*-values for test statistics, [b]analyzed with an ANOVA, leading to mean (*M*) and standard deviation (*SD*) and *F*-values for test statistics

Furthermore, analysis of variance showed a significant group difference in the volumes of right caudate nucleus, $F(2, 43) = 3.328$, $p < .05$ (Table 2). Independent samples t-tests indicated that volumes were significantly lower in children with CHD (M = 3'811 mm3, SD = 510 mm3) compared to the controls (M = 4'348 mm3, SD = 499 mm3), $t(26) = 2.79$, $p = .01$, $d = 1.07$. No significant differences were found in the volume of the caudate nucleus between children born very preterm (M = 4'104 mm3, SD = 612 mm3) and children with CHD $t(26) = -1.35$, $p = .19$, $d = -0.52$, or controls, $t(30) = 1.24$, $p = .23$, $d = 0.44$, respectively (Figure 10).

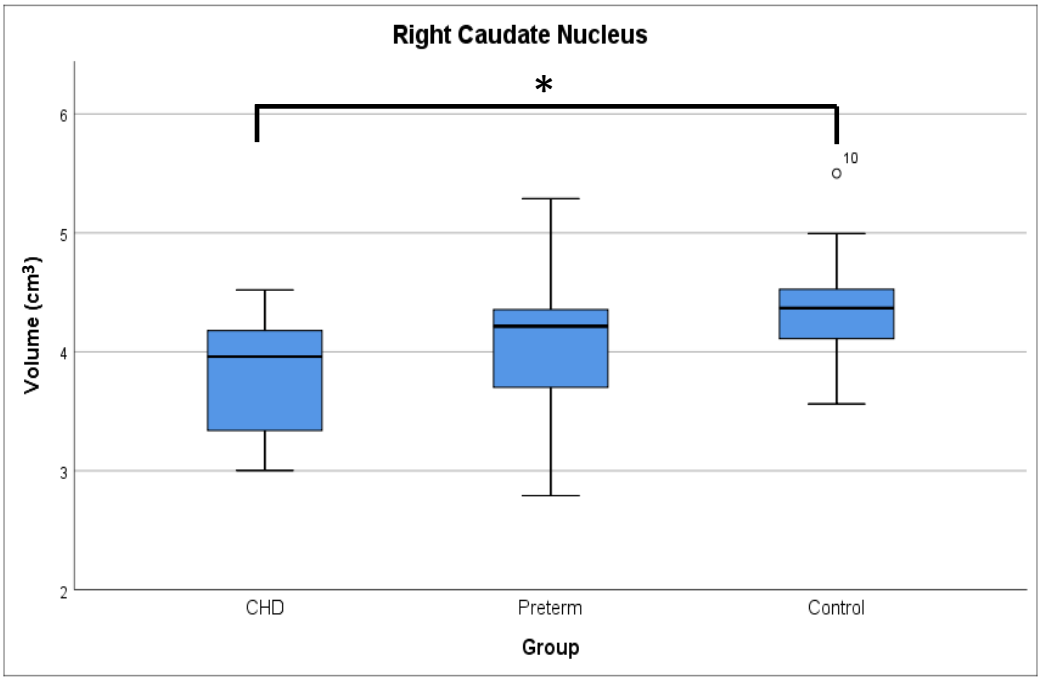

*Figure 10: Right Caudate Nucleus volumes in the white matter from each group with * indicating significant differences between the corresponding groups at a significance level of .05. Volumes are reported in cm^3.*

None of the other variables relating to the subcortical brain volumes differed significantly between the groups (Table 2). In the box plot for the right hippocampus (Figure 11), it appears that the hippocampus shows a tendency towards smaller volumes in children with CHD and children born very preterm compared with the healthy term-born children, but a Kruskal-Wallis test didn't reveal a significant group difference $H(2) = 3.715$, $p > .05$. Tendencies towards smaller subcortical brain volumes in the two clinical groups were also observed for nearly all the other volumetric measures from the subcortical structures (see Figure A 13 to Figure A 24 in the appendix).

The total brain volume (GM) did not differ significantly between the groups $F(2, 43) = 2.00$, $p > .05$, but tendencies towards smaller total brain volumes (GM) are evident from the means (Table 3).

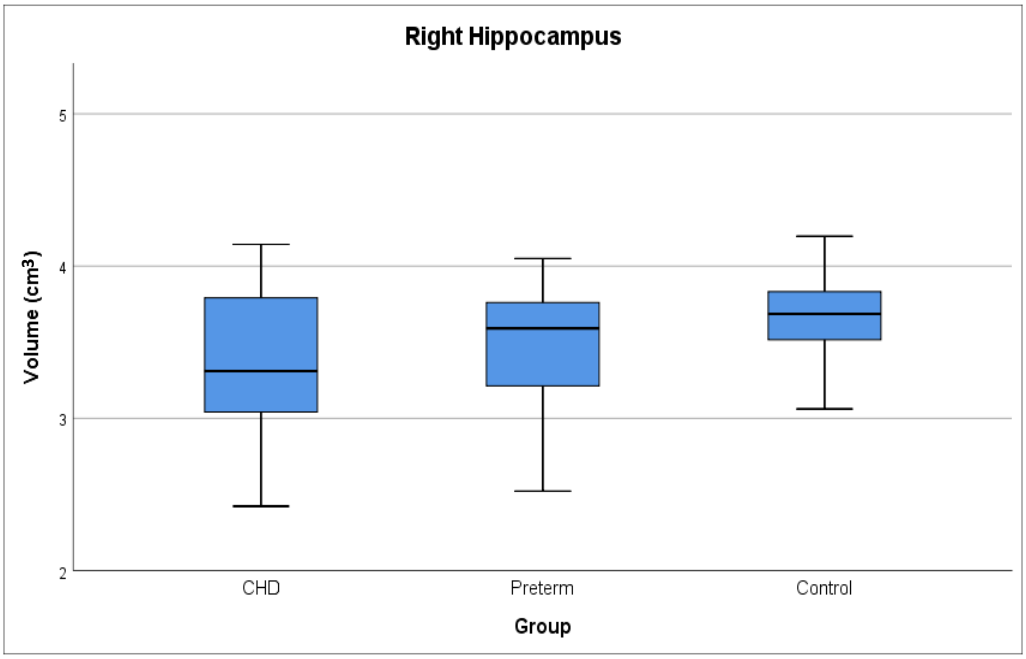

Figure 11: Right hippocampus volume from each group with no significant differences between the groups. Volumes are reported in cm^3.

Table 3: Sample size, mean and standard deviation (or median and range for non-normally distributed variables), test statistics and p-value of all the cortical brain volumes, volumes of prefrontal cortex and total brain volume (in mm3).

		CHD (*n* = 12) *M* (*SD*) / *Mdn* (range)	Preterm (*n* = 17) *M* (*SD*) / *Mdn* (range)	Control (*n* = 16) *M* (*SD*) / *Mdn* (range)	Test Statistics	*p*
Cortical Brain Volumes	GM					
	Left Hemisphere[b]	259'964 (31'154)	255'676 (32'461)	274'572 (28'207)	1.65	.21
	Right Hemisphere[b]	258'799 (30'907)	250'049 (37'184)	273'611 (28'132)	2.15	.13
	Total[b]	518'763 (61'874)	505'725 (69'033)	548'183 (56'198)	1.91	.16
	WM					
	Left Hemisphere[b]	188'113 (26'052)	188'132 (21'692)	199'657 (22'946)	1.24	.30
	Right Hemisphere[b]	188'694 (26'172)	186'039 (22'971)	201'088 (23'108)	1.76	.18
	Total[b]	376'807 (52'144)	374'172 (44'377)	400'745 (46'016)	1.49	.24
Prefrontal Cortex Volumes	Ventrolateral					
	Left Hemisphere[b]	13'456 (1'676)	12'536 (1'749)	14'267 (1'879)	3.80	.031
	Right Hemisphere[a]	13'851 (9'288 – 15'544)	11'752 (6'278 – 13'927)	13'927 (9'845 – 18'212)	13.29	.001
	Dorsolateral					
	Left Hemisphere[b]	50'474 (7'400)	51'605 (6'015)	53'926 (6'096)	1.07	.35
	Right Hemisphere[b]	51'008 (7'333)	51'691 (8'763)	55'414 (5'945)	1.51	.23
Total Brain Volume	GM					
	Total[b]	674'180 (73'772)	661'389 (73'393)	708'839 (62'791)	1.96	.16

GM: grey matter, WM: white matter, *n:* subsample size

[a]analyzed with a Kruskal-Wallis test, leading to median (*Mdn*) and *H*-values for test statistics, [b]analyzed with an ANOVA, leading to mean (*M*) and standard deviation (*SD*) and *F*-values for test statistics

3.3.1 Prefrontal Cortex (PFC)

In addition to the planned analyses for testing hypothesis 2 (comparison of subcortical volumes), analyses were also done for ventrolateral and dorsolateral PFC volumes separately (Table 3). Analysis of variance revealed a significant difference in the left ventrolateral PFC volume between the groups, $F(2, 43) = 3.80$, $p < .05$. Post-hoc analyses indicated smaller left ventrolateral PFC volumes in very preterm children (M = 50'877 mm^3, SD = 6'553 mm^3) than in controls (M = 53'926 mm^3, SD = 6'096 mm^3), $t(30) = 2.70$, $p = .01$, $d = 0.96$. No significant differences in the left ventrolateral PFC volume was found between children with CHD (M = 13'456 mm^3, SD = 1'676 mm^3) and very preterm children, $t(26) = 1.41$, $p = .17$, $d = 0.54$, or controls, $t(26) = 1.17$, $p = .25$, $d = 0.45$, respectively (Figure 12).

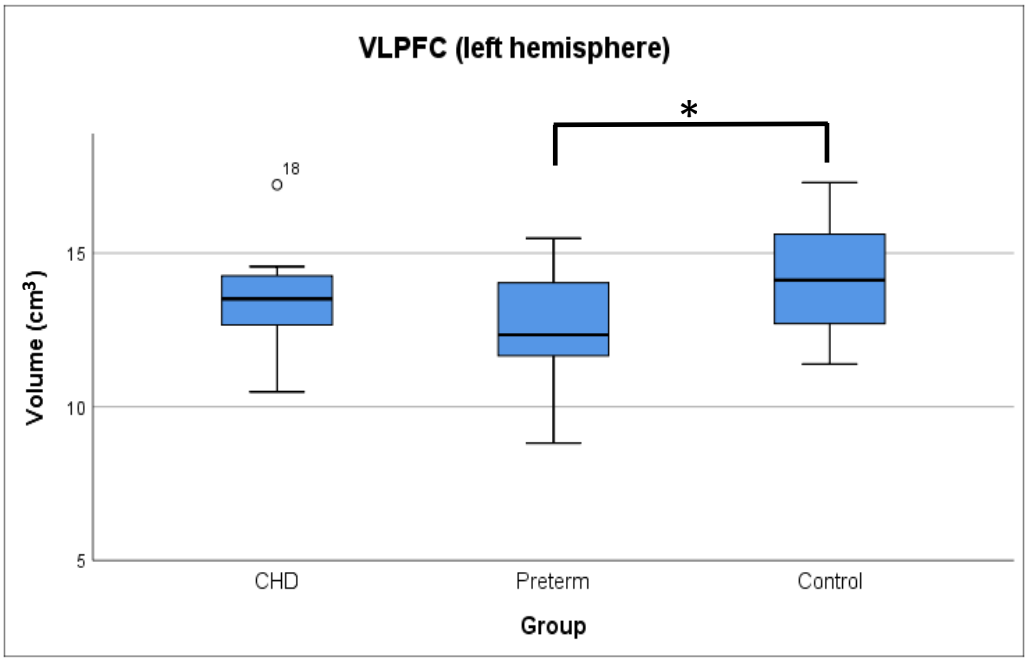

*Figure 12: Left hemisphere ventrolateral prefrontal cortex (VLPFC) volumes from each group with * indicating significant differences between the corresponding groups at a significance level of .05. Volumes are reported in cm^3.*

Ventrolateral PFC volumes also differed between the groups in the right hemisphere, $H(2) = 13.29$, $p < .05$ (Table 3). Mann-Whitney tests were used to follow up this finding. It appeared that right ventrolateral PFC volume was smaller in very preterm children compared to children with CHD ($U = 45.00$, $p = .02$, $d = 1.00$) as well as compared to the controls ($U = 33.00$, $p = .00$, $d = 1.64$). No significant difference in the right ventrolateral PFC volume was observed between children with CHD and controls ($U = 81.50$, $p = .51$ $d = 0.26$) (Figure 13).

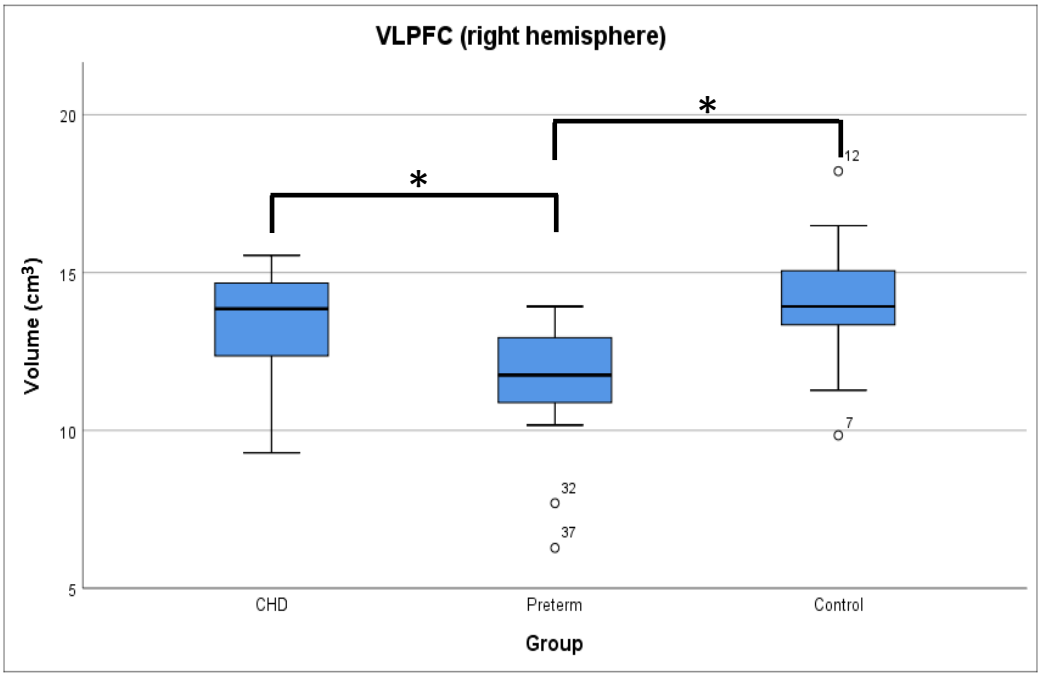

*Figure 13: Right hemisphere ventrolateral prefrontal cortex (VLPFC) volumes from each group with * indicating significant differences between the corresponding groups at a significance level of .05. Volumes are reported in cm^3.*

3.4 Hypothesis 3 (Correlations of EF Outcome and Brain Volumes)

Table 4 reports the bivariate correlations for the EF outcome with subcortical brain volumes. As seen, a higher Backwards Span Length in the Corsi Block Tapping Task was associated with a larger right hippocampus and a larger left putamen as well as larger volumes in the pallidum and total subcortical GM. A higher Number of Correct Sequences in the Digit Span Test was associated with larger volumes in the left cerebellar GM and the hippocampus as well as larger volumes in the putamen and total subcortical GM (Table 4).

Table 4: Correlations of EF outcome with subcortical brain volumes

			Subcortical Brain Volumes														
			Cerebellum				Thalamus		Hippocampus		Basal Ganglia						GM
			WM Left	WM Right	GM Left	GM Right	Left	Right	Left	Right	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Pallidum Left	Pallidum Right	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.34*	.32*	.12	.11	.29	.24	.31*	.38*	.12	.21	.44**	.45**	.51**	.45**	.46**
		Highest Span Length (forwards)	.18	.20	.08	.08	.24	.11	.18	.26	.05	.11	.40**	.41**	.41**	.31*	.36*
		Number of Correct Sequences (backwards)	.28	.23	.01	.01	.28	.31*	.31*	.42**	.08	.17	.30*	.25	.41**	.37*	.33*
		Highest Span Length (backwards)	.22[a]	.20	.08[a]	.06[a]	.21[a]	.30[a]	.26[a]	.46**[a]	.07[a]	.11[a]	.31*[a]	.24[a]	.41**[a]	.35*[a]	.33*[a]
	TAP Working Memory	Number of Errors	-.21	-.28	-.15	-.29	-.13	.08	-.15	-.22	-.08	-.09	-.32*	-.42**	-.19	-.17	-.22
		Omissions	.19	.09	.16	.14	-.02	-.13	-.11	-.08	.10	.12	-.28	-.14	-.01	-.07	-.08
	Digit Span Test	Number of Correct Sequences	.23[a]	.24	.36*[a]	.27[a]	.22[a]	.07[a]	.32*[a]	.32*[a]	.10[a]	.16[a]	.43**[a]	.49**[a]	.25[a]	.23[a]	.34*[a]
Flexibility	TAP Flexibility	Number of Errors	-.19	-.35*	-.08	-.07	-.10	-.08	-.25	-.22	-.22	-.28	-.25	-.27	-.13	-.14	-.22
		Reaction Time	-.31*	-.30*	-.03	.00	-.31*	-.41**	-.36*	-.43**	-.14	-.26	-.41**	-.39**	-.39**	-.48**	-.42**
	RWT	Number of Words, 1st Minute (Percentile Rank)	-.19	-.07	.11	.03	-.20	-.26	-.11	-.05	.00	-.09	-.25	-.18	-.19	-.29	-.23
		Number of Words, 2nd Minute (Percentile Rank)	-.28[a]	-.22	-.24[a]	-.28[a]	-.35*[a]	-.29[a]	-.27[a]	-.25[a]	-.20[a]	-.26[a]	-.21[a]	-.22[a]	-.39**[a]	-.46**[a]	-.36*[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	.05	-.01	.06	.27	-.25	-.21	-.17	-.18	-.07	-.10	-.12	.04	.00	-.08	-.14
		Time-Per-Move Ratio	.12	-.01	-.04	.03	-.07	-.07	.14	.10	-.02	-.02	.19	.15	.07	.03	-.01
		Move Accuracy Ratio	.22	.28	.16	.31	.07	.02	.09	.03	.27	.25	.15	.23	.19	.11	.19

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

Furthermore, there were negative correlations between the Reaction Time in the Flexibility subtest of TAP and volumes in the cerebellum and thalamus as well as volumes in the hippocampus and all the basal ganglia except the caudate nucleus. The Reaction Time was also correlated with larger total subcortical GM volume. These correlations between the EF domains working memory or cognitive flexibility with various subcortical brain volumes indicate that children with poorer performance in working memory and cognitive flexibility typically have smaller subcortical brain volumes. For the visual-spatial planning, no variable was correlated with any subcortical brain volumes (Table 4).

After doing the calculations for the three groups separately, the correlations between the performances in the backwards condition in the Corsi Block Tapping Task and the hippocampal volume as well as volumes in the putamen and the pallidum only remained significant in the group of very preterm children (see Table A 8 in the appendix). Table A 4 and Table A 8 in the appendix also show that the correlations between the Reaction Time in the Flexibility subtest of TAP and the subcortical brain volumes disappeared for the very preterm children and the controls after doing the calculations for the three groups separately.

Table 5 reports the bivariate correlations for EF outcome with cortical and total brain volumes. Higher Backwards Span Length in the Corsi Block Tapping Task was correlated with a larger cortex, a larger PFC and greater total brain volumes. In addition, better outcome in the Digit Span Test was associated with larger volumes in all the subcortical brain regions. Positive correlations between the EF outcome and the cortical and total brain volume were also found for all the other EF domains: For cognitive flexibility, better performance in TAP (lower reaction time) was correlated with a larger cortex, a larger PFC and larger total brain volumes. Also, visual-spatial planning correlated positively with the left ventrolateral PFC (Table 5).

Table 5: Correlations for EF outcomes with cortical and total brain volumes

			Cortical Brain Volumes						Prefrontal Cortex Volumes				Total Brain Volume
			GM			WM			Ventrolateral		Dorsolateral		GM
			LH	RH	Total	LH	RH	Total	LH	RH	LH	RH	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.61**	.58**	.59**	.64**	.63**	.63**	.34*	.33*	.49**	.47**	.58**
		Highest Span Length (forwards)	.49**	.46**	.47**	.55**	.52**	.53**	.21	.22	.38*	.33*	.46**
		Number of Correct Sequences (backwards)	.45**	.41**	.43**	.51**	.49**	.50**	.27	.33*	.36*	.39**	.40**
		Highest Span Length (backwards)	.46**[a]	.46**[a]	.46**[a]	.45**[a]	.47**[a]	.46**[a]	.31*[a]	0.36*	.35*[a]	.45**[a]	.45**[a]
	TAP Working Memory	Number of Errors	-.27	-.29	-.28	-.24	-.26	-.25	-.26	-.23	-.31*	-.26	-.32*
		Omissions	.03	.08	.07	-.06	-.05	-.05	-.10	-.13	.11	.13	.07
	Digit Span Test	Number of Correct Sequences	.53**[a]	.51**[a]	.52**[a]	.412**[a]	.41**[a]	.42**[a]	.33*[a]	.35*	.40**[a]	.42**[a]	.54**[a]
Flexibility	TAP Flexibility	Number of Errors	-.32*	-.26	-.28	-.25	-.21	-.23	-.34*	-.36*	-.23	-.17	-.28
		Reaction Time	-.56**	-.56**	-.56**	-.54**	-.59**	-.56**	-.35*	-.44*	-.54**	-.58**	-.53**
	RWT	Number of Words, 1st Minute (Percentile Rank)	-.11	-.11	-.11	-.27	-.25	-.26	.12	-.01	-.20	-.14	-.13
		Number of Words, 2nd Minute (Percentile Rank)	-.19[a]	-.15[a]	-.17[a]	-.29[a]	-.27[a]	-.28[a]	.01[a]	-.07[a]	-.25	-.15[a]	-.22[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	.01	.03	.02	-.17	-.13	-.16	.09	.14	-.04	-.01	.03
		Time-Per-Move Ratio	.16	.18	.18	.07	.10	.10	-.01	.20	.16	.16	.17
		Move Accuracy Ratio	.18	.16	.15	.01	.01	.0	.45**	.30	.07	.07	.18

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, LH: left hemisphere, RH: right hemisphere, GM: grey matter, WM: white matter

[a]Pearson's r, Spearman's r if not special labeled, ***$p < .001$, **$p < .01$, *$p < .05$

After doing the calculations for the three groups separately, the correlations between the Highest Backwards Span Length in the Corsi Block Tapping Task and the cortical brain volumes disappeared in the children with CHD and the control group. Also, the correlations between the outcome in the Digit Span Test and cortical brain volumes only remained significant in the group of the very preterm children, except one correlation between the Number of Correct Sequences and the volume of right dorsolateral PFC, which was still significant in the control group. For the visual-spatial planning, positive correlations between the Move Accuracy Ratio and cortical as well as prefrontal cortical and total brain volumes was revealed in the children with CHD (see Table A 5, Table A 7 and Table A 9 in the appendix).

Again, these correlations between variables of all the three EF domains and cortical as well as total brain volumes indicate that children with worse performances in EF tests have smaller cortical and total brain volumes.

However, one exception to this trend was observed in the correlations between the variables of the RWT and the subcortical brain volumes. These correlations went in the opposite direction in that smaller subcortical brain volumes were associated with better performance in cognitive flexibility assessed with RWT (Table 4). Some more EF variables with correlations indicating a negative association between EF outcomes and brain volumes appeared after doing the calculations for the three groups separately: Higher scores in the Total Achievement Score and Time-Per-Move Ratio assessed with the Tower Test were correlated with smaller volumes in subcortical as well as cortical brain structures, but only in the control group (see Table A 4 and Table A 5 in the appendix).

4. Discussion

The aim of this master's thesis was to directly compare children with CHD and very preterm children regarding their executive functions and subcortical and total brain volumes and to investigate if and to what extent these two clinical groups differ from each other in these outcomes. Results were also compared to a third group of healthy term-born children. The EF were assessed with commonly used neurodevelopmental tests while brain volumes were measured with MRI. Statistical analysis revealed poorer performance in working memory in both clinical groups compared to the control group. Furthermore, there were smaller subcortical and prefrontal cortical brain volumes in children with CHD, or very preterm children, respectively compared to healthy term-born children. Poorer EF outcome was further correlated with larger brain volumes.

4.1 Hypothesis 1

Several studies reported impaired executive functions in children with CHD (Bellinger et al., 2003; Cassidy et al., 2015; Schaefer et al., 2013) and in very preterm born children (Anderson & Doyle, 2004; Luciana et al., 1999; Luu et al., 2011; Ritter et al., 2013; Saavalainen et al., 2007) compared to healthy term-born controls. Hypothesis 1 thus postulated similar EF deficits in children with CHD and very preterm children compared to a healthy term-born control group.

In the present study, the only EF domain which showed significant differences between the two clinical groups and the controls was that of visual-spatial working memory, as children with CHD and very preterm children performed worse than the controls in the Corsi Block Tapping Task. This is consistent with the findings of Luciana et al. (1999) and Saavalainen et al. (2007) who also reported worse performance in working memory assessed with a task based on the Corsi Block Tapping Task in preterm children. Considering that the subgroup of very preterm children in this work was older than the control group, this difference in performance is even more pronounced, since performance in working memory should increase with age (Gathercole, Pickering, Ambridge, & Wearing, 2004).

Impaired working memory was reported in children with CHD too, but Schaefer et al. (2013) found these results in the Digit Span Test (i.e., verbal working memory). In contrast, this work didn't find poorer performance in verbal working memory both, in children with CHD and very preterm children compared to the controls. One reason could be that the children included in the study of Schaefer et al. (2013) were older (11 to 16 years) than the children in this work (9 to 11 years), so maybe impairments in the verbal domain of working memory only are manifested in the later adolescence. However, Anderson & Doyle (2004) reported poorer performance in the Digit Span Test in very preterm children, who were at a similar age (8 to 9

years) as the children in this work are. It must therefore be assumed that the absence of significant group differences in verbal working memory in this work is due to the small sample size.

No significant differences could be reported for the EF domains cognitive flexibility and visual-spatial planning. For the cognitive flexibility, all the studies, which are reported in this work and which revealed impaired cognitive flexibility in children with CHD (Bellinger et al., 2011; Cassidy et al., 2015) or very preterm children (Luu et al., 2011; Ritter et al., 2013) compared to controls, assessed cognitive flexibility with the Trail Making Test or Sorting Test (subtests of the D-KEFS (Delis et al., 2001)). Maybe the tests assessing cognitive flexibility (RWT and TAP) used in this work were not sensitive enough to reveal differences between children with CHD or very preterm children and the controls respectively

Also, for the visual-spatial planning, the test with which this ability was assessed for this thesis is probably a reason for the absent group differences. There were many missing values in the variables relating to visual-spatial planning assessed through the Tower Test. The Tower Test is very vulnerable to test leader errors and it is therefore not advisable to assess visual-spatial planning with only this test when such a small sample size is examined. An additional method to collect some information in this domain may be an interview of the parents and teachers about the children's visual-spatial planning abilities. Toplak and colleagues (2013) have demonstrated the importance of assessing a cognitive function through different tools. As performance-based and rating measures of EF assess different aspects of the cognitive function, they can provide a more comprehensive understanding of an EF domain in the examined individual when they are applied in combination (Toplak, West, & Stanovich, 2013).

While this work identified only a few significant differences between groups (as discussed in detail in subsection 4.4), a tendency in the hypothesis-conform direction, indicating slightly poorer performance in both, children with CHD and very preterm children compared to the controls, was seen across all EF domains.

Nevertheless, hypothesis 1 could be confirmed to the extent that the two clinical groups didn't differ from each other in any of the EF variables, and in particular they had similar problems in visual-spatial working memory compared to the control group. Whether these problems can already be described as deficits is not quite clear in this work. Since there are no norms for the Corsi Block Tapping Task, one cannot judge whether the performances of these children fall within a clinically relevant range. However, both groups represent subpopulations which are at similarly increased risk for impairments in EF, particularly visual-spatial working memory.

4.2 Hypothesis 2

The second hypothesis of this work was that there are similarly reduced volumes in subcortical brain structures and whole brain in children with CHD and very preterm children compared to the control group. This hypothesis could not be confirmed because although there were significant differences between children with CHD and the controls, and between very preterm children and the controls, the reduced brain volumes in the two clinical groups compared to the controls were shown in different brain regions.

Smaller volumes in left cerebellar WM were only found between children with CHD and the controls whereas children born very preterm didn't differ from the control group. Von Rhein et al. (2013) also reported smaller cerebellar volumes in children with CHD, but they found *total* smaller cerebellar volumes and didn't compare them to children born very preterm. Nevertheless, the smaller cerebellar WM volume in children with CHD found in this work can be compared to the study findings by Taylor et al. (2011) who reported smaller cerebellar WM in very preterm children.

In addition, this work revealed smaller subcortical brain volumes in the right caudate nucleus in children with CHD compared to the controls. This finding is in line with the results of von Rhein et al. (2013) who also reported smaller volumes in the basal ganglia in children with CHD compared to healthy controls. Whether von Rhein and colleagues found these smaller volumes specifically in the caudate nucleus is not mentioned. For the very preterm children, the findings of smaller volumes in the caudate nucleus, as reported by Nosarti et al. (2008), could not be replicated in this work. Again, one reason could be the small sample size in this work with 16 children in the group of very preterm children and the control group respectively. As a comparison: Nosarti and her team (2008) found the smaller volumes in the caudate nucleus in a subsample of 90 very preterm children.

The second part of hypothesis 2 was about the total brain volume, which was not significantly different between the three groups. In comparison, Nosarti at al. (2008) and Taylor et al. (2011) revealed reduced total brain volumes in very preterm children compared to term-born children. Also, von Rhein et al. (2013) reported similar findings for children with CHD compared to healthy children. The fact, that no reduced total brain volumes were found between the two clinical group and the control group in this work is probably due to different structures which were used as an indicator for total brain volume. This work used the total GM as such an indicator whereas Nosarti et al. (2008) or von Rhein et al. (2013) included several other structures among the total GM (such as the cerebellum or total WM) for calculating the total brain volume. Therefore, hypothesis 2 could not be confirmed with the analysis in this thesis. Further analysis would be necessary, using the same structures as an indicator for total brain volume as Nosarti et al. (2008) and von Rhein et al. (2013) were using.

As the PFC was shown to play a particularly important role in EF (Baker et al., 1996; Grattan & Eslinger, 1991; Morris et al., 1993; Rezai et al., 1993; Stuss & Benson, 1984; Yuan & Raz, 2014), additional analyses were done for this brain structure, leading to significant results with the ventrolateral PFC being smaller in very preterm children compared to the controls. As there was also a significantly smaller volume in the right ventrolateral PFC in very preterm children compared to children with CHD, this structure seems to be affected specifically in very preterm children but not in children with CHD. Although the difference in the right ventrolateral PFC between the two clinical groups was significant (p = .02) and the effect size of this analysis was high (d = 1.00), this group difference should be considered with caution. None of the reported studies also examined the volume of PFC in the two clinical groups, so it would be too hasty to suggest that the cerebellum is in general more affected in children with CHD than in very preterm children and further studies must be conducted in the future to confirm this finding.

4.3 Hypothesis 3

An association between poorer EF performance and smaller brain volumes was already shown both in children with CHD (Latal et al., 2016; von Rhein et al., 2013) as well as in children born very preterm (Nosarti et al., 2008; Taylor et al., 2011). Therefore, hypothesis 3 assumed that there is a correlation between brain volumes and EF.

Most of the significant correlations between EF performance and different brain volumes in this master's thesis were found for the EF domain working memory. Poorer Corsi Block Tapping Task performance was correlated with smaller volumes in the right hippocampus and left putamen as well as in the pallidum and the subcortical GM. Furthermore, there were positive correlations between the performance in Corsi Block Tapping Task and all the cortical brain volumes. Better performance in the Digit Span Test assessing verbal working memory was associated with larger subcortical and cortical brain volumes too.

Correlations between smaller brain volumes and poorer working memory performance have also been reported in the literature, particularly in children with CHD (Latal et al., 2016; von Rhein et al., 2013). Latal and her team (2016) found positive correlations between the verbal working memory assessed with the Digit Span Test and the hippocampal volume but only in children with CHD and not in the control group (Latal et al., 2016). An association between working memory and hippocampal volume was also reported in (very) preterm born infants and adults (Aanes, Bjuland, Skranes, & Løhaugen, 2015; Beauchamp et al., 2008). However, in the sample of this thesis, correlations between the highest Backwards Span Length in the Corsi Block Tapping Task and subcortical (right hippocampus, left putamen and right pallidum) as well as cortical brain volumes only remained for the very preterm children

but not for the children with CHD after doing the calculations for the groups separately. This finding could lead to the suggestion, that the impairments in the visual-spatial working memory are based on different neuronal correlates in children with CHD and very preterm children, but this should be considered with caution as the sample size was very small in this work and thus outliers could lead to biased correlations.

Overall correlations with brain volumes were found in all the EF domains in at least one variable. However, remarkably few correlations were observed between the EF domain visual-spatial planning and brain volumes. This may be caused to the fact that there were many missing values in the variables of the Tower Test, as already discussed in chapter 4.1.

Nevertheless, almost all the correlations were in the direction that better performance was associated with larger brain volumes. An exception were the correlations between the RWT variables and subcortical brain volumes with higher performance in RWT associated to smaller volumes in the left thalamus and the pallidum.

4.4 Limitations

Overall this master's thesis could only report a few significant differences between the two clinical groups and the control group, especially within the EF variables. This may be mainly due to the small sample size in this in this work. In addition, single missing values exert a large effect in such small sample sizes, as already discussed in the context of the Tower Test in chapter 4.1.

Another limitation of this work is that results were not controlled for socioeconomic status (SES). This decision was made because the sample size was already quite small and therefore it was not appropriate to control for SES. But as most of the control children were recruited at the Children's University, it is possible that these children have parents with an academic background and therefore live in families with a high SES. This may have led to better performance in the control group and differences may not be solely related to CHD or prematurity. Nevertheless, the aim of this thesis was to compare the two clinical groups directly and it can be expected that these two groups should not differ from each other regarding SES, as they were recruited due to their clinical relevance out of a clinical study pool.

Furthermore, this work didn't differ between children treated as neonates with and without erythropoietin (Epo) in the subpopulation of very preterm children. In order to consider the influence of Epo on the results, the ongoing EpKids study would have had to be unblinded for this thesis, which was not possible. Nevertheless, if Epo is associated with a positive effect on EF and brain development, this would speak even more for the results of this work, as children with Epo would have increased the mean in EF performance in the very preterm subgroup.

4.5 Further Investigation

This work provides a first comparison between the two clinical groups of children with CHD and very preterm children. Similarities in the apparent deficits compared to healthy term-born children could be found in visual-spatial working memory – an ability which is impaired in both clinical groups. Although there are several studies showing impairments in the verbal working memory, the cognitive flexibility and the visual-spatial planning in those groups (Anderson & Doyle, 2004; Cassidy et al., 2015; Ritter et al., 2013; Schaefer et al., 2013), it might be that the visual-spatial working memory domain is more vulnerable for impairments than other EF domains and therefore was the only EF domain which was revealed impaired in children with CHD and very preterm children in this work. Intact hippocampi were shown to be crucial for visual-spatial working memory (van Asselen et al., 2006). The positive correlation between performance in visual-spatial working memory and hippocampal volume in very preterm children in this work leads to the suggestion that particularly the hippocampus could be vulnerable for early disruptions in brain maturation. However, this is only an assumption and should be examined more precisely through further studies.

Considering that deficits in EF have a strong impact on learning skills and may underlie the frequent academic problems reported in school-aged children (Mulder, Pitchford, & Marlow, 2010), it is important to have a precise understanding about the relationships between very preterm birth or suffering from CHD and EF respectively. In order to facilitate the entrance into school and later job for these two risk populations, it is important to be aware of such EF deficits and train these abilities early in life. Based on the results revealed in thesis, the same potential assessments which would train visual-spatial working memory could be applied for both groups.

Nevertheless, further investigation should compare these two clinical groups in more detail and with larger sample sizes, since findings of similar deficits in EF could lead to the development of preventive strategies and possible interventions for both of these two clinical groups. Above all, knowledge about the underlying mechanisms and the neurodevelopmental basis is of great importance and must be further investigated.

5. Conclusion

This master's thesis revealed similar problems in visual-spatial working memory in children with CHD and children born very preterm. It is possible that these problems may share a common cause in the form of delayed maturation of the brain as this work showed smaller volumes in cerebellar WM in children with CHD and smaller ventrolateral PFC volume for very preterm children respectively. However, while the impaired visual-spatial working memory in very preterm children was shown to be associated with smaller subcortical and cortical volumes, evident neuronal correlates for the impaired working memory in children with CHD were not found in this work. Thus, it seems that the EF impairments in children with CHD and very preterm children are likely to have different neural underpinnings.

However, similarities or differences between these two clinical groups are still quite unclear. Therefore, further studies must be conducted to build a more precise picture of possible EF deficits in these two clinical groups. If the potential underlying neurodevelopmental factors are clearly identified, preventive strategies and possible therapeutic interventions could be developed in order to guarantee adequate support and care for the children and their families.

6. Bibliography

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7. Appendix

7.1 Tests for Normal Distribution in the EF Variables (Table A 1)

	Group	Shapiro-Wilk		
		Statistic	df	Significance
Corsi Block Tapping Task: Number of Correct Sequences (forwards)	Control	0.89	16	.046
	CHD	0.89	12	.11
	Preterm	0.92	17	.17
Corsi Block Tapping Task: Highest Span Length (forwards)	Control	0.93	16	.22
	CHD	0.90	12	.16
	Preterm	0.86	17	.015
Corsi Block Tapping Task: Number of Correct Sequences (backwards)	Control	0.94	16	.34
	CHD	0.93	12	.38
	Preterm	0.88	17	.032
Corsi Block Tapping Task: Highest Span Length (backwards)	Control	0.96	16	.58
	CHD	0.88	12	.081
	Preterm	0.93	17	.21
TAP (Working Memory): Number of Errors	Control	0.79	15	.003
	CHD	0.79	12	.007
	Preterm	0.82	17	.004
TAP (Working Memory): Omissions	Control	0.91	15	.13
	CHD	0.78	12	.005
	Preterm	0.93	17	.23
Digit Span Test: Number of Correct Sequences	Control	0.95	15	.53
	CHD	0.88	12	.091
	Preterm	0.98	17	.98
TAP (Flexibility): Number of Errors	Control	0.91	15	.16
	CHD	0.90	12	.15
	Preterm	0.87	17	.02
TAP (Flexibility): Reaction Time (ms)	Control	0.94	16	.4
	CHD	0.84	12	.029
	Preterm	0.95	17	.51
RWT: Number of Words (1st Minute) in Percentile Rank	Control	0.91	16	.11
	CHD	0.94	12	.50
	Preterm	0.89	17	.047
RWT: Number of Words (2nd Minute) in Percentile Rank	Control	0.93	16	.22
	CHD	0.88	12	.076
	Preterm	0.92	17	.18
Tower Test: Total Achievement Score (Scaled Score)	Control	0.93	12	.36
	CHD	0.73	9	.004
	Preterm	0.92	15	.17
Tower Test: Time-Per-Move Ratio	Control	0.90	12	.17
	CHD	0.71	9	.002
	Preterm	0.90	15	.10
Tower Test: Move Accuracy Ratio	Control	0.94	12	.48
	CHD	0.80	9	.019
	Preterm	0.95	15	.54

7.2 Tests for Normal Distribution in the Brain Volume Variables (Table A 2)

	Group	Shapiro-Wilk		
		Statistik	df	Signifikanz
Left Cerebellar WM	Control	0.93	16	.21
	CHD	0.93	12	.34
	Preterm	0.96	16	.69
Right Cerebellar WM	Control	0.97	16	.89
	CHD	0.92	12	.33
	Preterm	0.94	16	.35
Left Cerebellar GM	Control	0.96	16	.58
	CHD	0.94	12	.49
	Preterm	0.93	16	.23
Right Cerebellar GM	Control	0.98	16	.92
	CHD	0.96	12	.83
	Preterm	0.90	16	.075
Left Thalamus	Control	0.95	16	.54
	CHD	0.95	12	.66
	Preterm	0.98	16	.92
Right Thalamus	Control	0.95	16	.50
	CHD	0.94	12	.45
	Preterm	0.97	16	.81
Left Hippocampus	Control	0.96	16	.67
	CHD	0.97	12	.91
	Preterm	0.96	16	.67

	Group	Shapiro-Wilk		
		Statistik	df	Signifikanz
Right Hippocampus	Control	0.98	16	.94
	CHD	0.97	12	.94
	Preterm	0.93	16	.27
Left Caudate Nucleus	Control	0.94	16	.32
	CHD	0.93	12	.35
	Preterm	0.96	16	.62
Right Caudate Nucleus	Control	0.96	16	.58
	CHD	0.88	12	.19
	Preterm	0.97	16	.88
Left Putamen	Control	0.97	16	.91
	CHD	0.91	12	.22
	Preterm	0.94	16	.36
Right Putamen	Control	0.98	16	.94
	CHD	0.90	12	.18
	Preterm	0.96	16	.63
Left Pallidum	Control	0.95	16	.56
	CHD	0.91	12	.24
	Preterm	0.95	16	.43
Right Pallidum	Control	0.94	16	.37
	CHD	0.93	12	.44
	Preterm	0.96	16	.71

	Group	Shapiro-Wilk		
		Statistik	df	Signifikanz
Subcortical GM	Control	0.91	16	.098
	CHD	0.96	12	.85
	Preterm	0.97	16	.80
Cortical GM (left hemisphere)	Control	0.97	16	.79
	CHD	0.97	12	.90
	Preterm	0.94	16	.30
Cortical GM (right hemisphere)	Control	0.95	16	.43
	CHD	0.95	12	.66
	Preterm	0.95	16	.54
Total Cortial GM	Control	0.96	16	.60
	CHD	0.96	12	.74
	Preterm	0.95	16	.55
Cortical WM (left hemisphere)	Control	0.96	16	.63
	CHD	0.98	12	.97
	Preterm	0.95	16	.50
Cortical WM (right hemisphere)	Control	0.95	16	.51
	CHD	0.97	12	.87
	Preterm	0.97	16	.85

	Group	Shapiro-Wilk		
		Statistik	df	Statistik
Total Cortical WM	Control	0.96	16	.57
	CHD	0.97	12	.94
	Preterm	0.97	16	.84
Left Ventrolateral Prefrontal Cortex	Control	0.95	16	.53
	CHD	0.95	12	.64
	Preterm	0.96	16	.64
Right Ventrolateral Prefrontal Cortex	Control	0.96	16	.65
	CHD	0.88	12	.078
	Preterm	0.86	16	.020
Left Dorsolateral Prefrontal Cortex	Control	0.96	16	.66
	CHD	0.96	12	.85
	Preterm	0.95	16	.42
Right Dorsolateral Prefrontal Cortex	Control	0.94	16	.40
	CHD	0.96	12	.85
	Preterm	0.93	16	.22
Total Brain (GM)	Control	0.94	16	.31
	CHD	0.96	12	.81
	Preterm	0.96	16	.72

7.3 Tests for Variance Homogeneity in the Normally Distributed Variables (Table A 3)

	Levene Statistic	df1	df2	Signifi-cance
Corsi Block Tapping Task: Highest Span Length (backwards	0.03	2	41	.98
Digit Span Test: Number of Correct Sewuences	0.45	2	41	.64
RWT: Number of Words (2nd Minute)	0.49	2	41	.61
Left Cerebellar WM	1.44	2	41	.25
Right Cerebellar WM	6.32	2	41	.004
Left Cerebellar GM	1.19	2	41	.32
Right Cerebellar GM	0.48	2	41	.62
Left Thalamus	0.27	2	41	.77
Right Thalamus	0.03	2	41	.97
Left Hippocampus	0.16	2	41	.86
Right Hippocampus	1.75	2	41	.19
Left Putamen	2.61	2	41	.086
Right Putamen	0.51	2	41	.60
Left Pallidum	0.11	2	41	.90
Right Pallidum	0.43	2	41	.66

	Levene Statistic	df1	df2	Signifi-cance
Left Caudate	0.58	2	41	.56
Right Caudate	0.38	2	41	.69
Subcortical GM	0.12	2	41	.89
Cortical GM (left hemisp-here)	0.87	2	41	.43
Cortical GM (right hemisp-here)	1.51	2	41	.23
Total Cortical GM	1.10	2	41	.34
Cortical WM (left hemisp-here)	0.25	2	41	.78
Cortical WM (right hemisp-here)	0.21	2	41	.81
Total Cortical WM	0.23	2	41	.80
Left Ventrolateral Prefron-tal Cortex	0.46	2	41	.64
Left Dorsolateral Prefrontal Cortex	0.22	2	41	.81
Right Dorsolateral Prefron-tal Cortex	1.35	2	41	.27
Total Brain (GM)	1.07	2	41	.35

7.4 Box Plots for Non-Significant Differences in Working Memory Performance

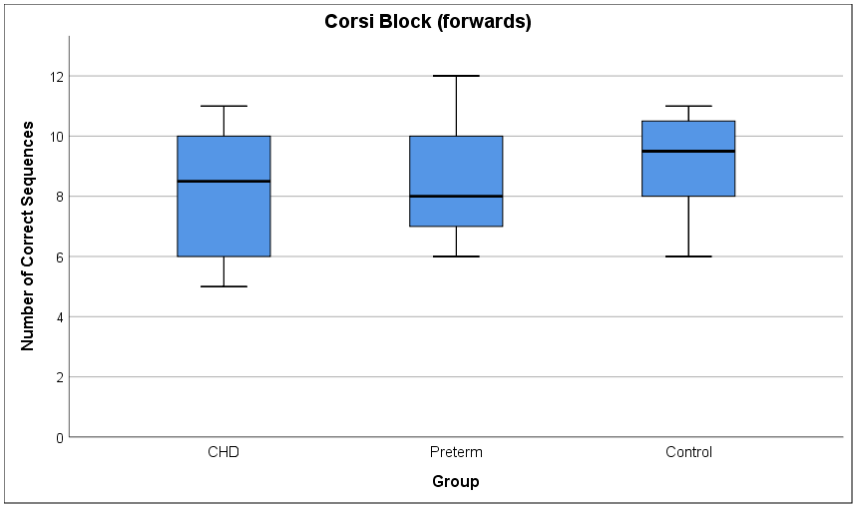

Figure A 1: Number of Correct Sequences in the forward condition of Corsi Block Tapping Task for each group with no significant differences between the groups

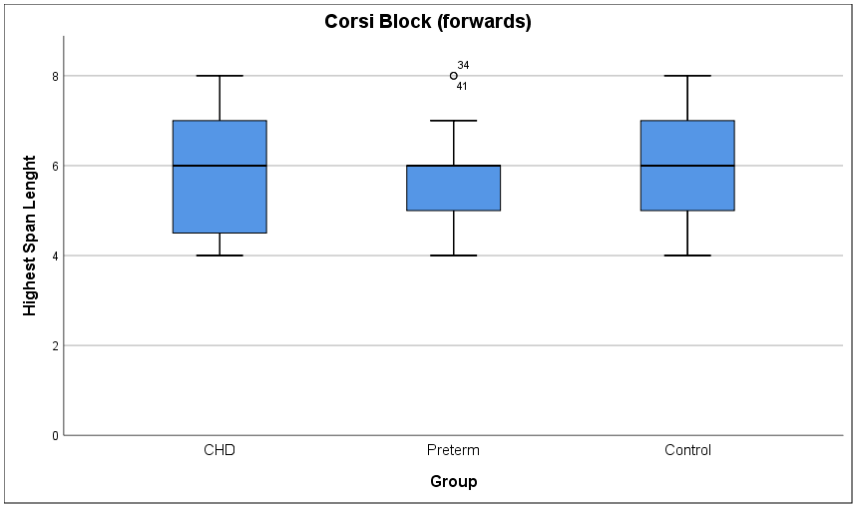

Figure A 2: Highest Span Length in the forward condition of Corsi Block Tapping Task for each group with no significant differences between the groups

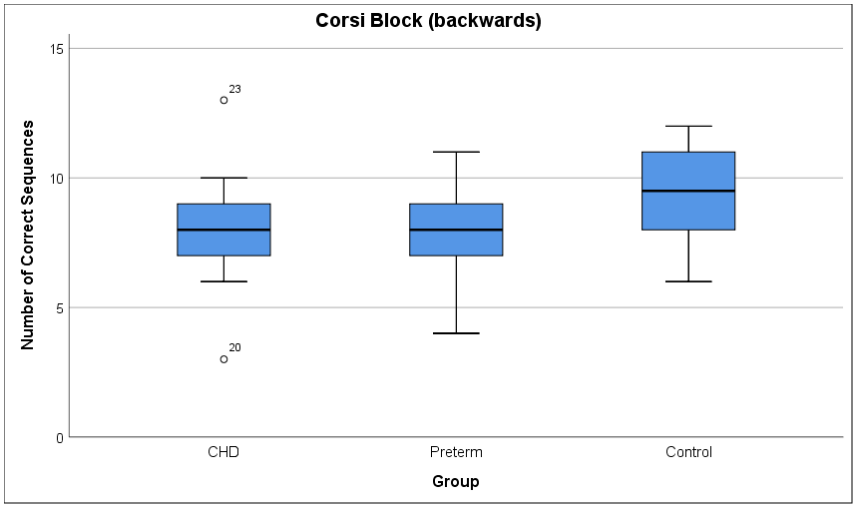

Figure A 3: Number of Correct Sequences in the backwards condition of Corsi Block Tapping Task for each group with no significant differences between the groups

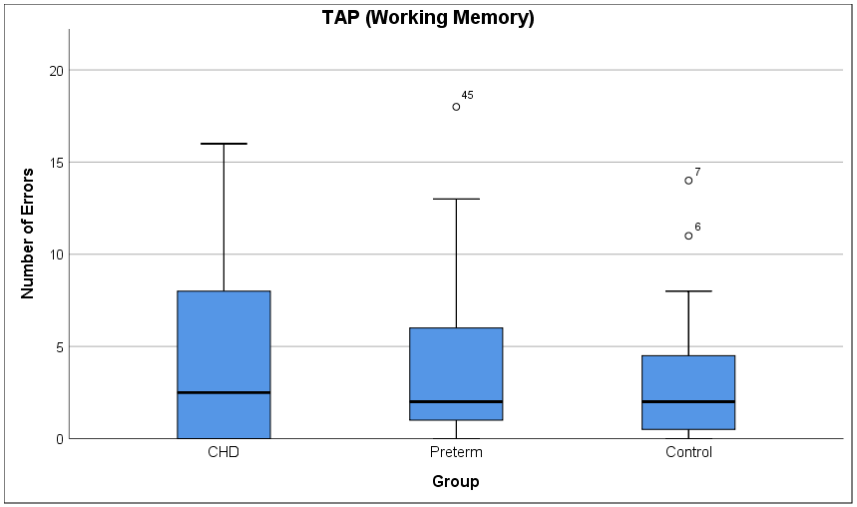

Figure A 4: Number of Errors in the Working Memory subtest of the TAP for each group with no significant differences between the groups

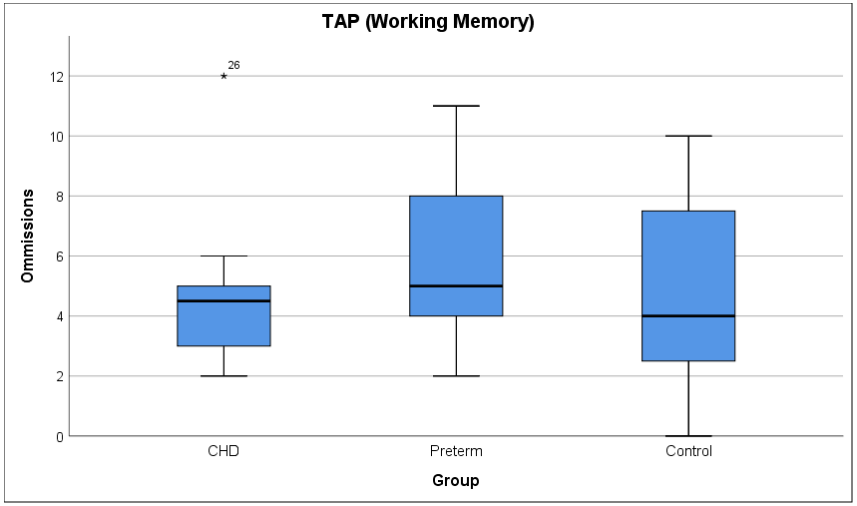

Figure A 5: Number of Omissions in the Working Memory subtest of TAP for each group with no significant differences between the groups

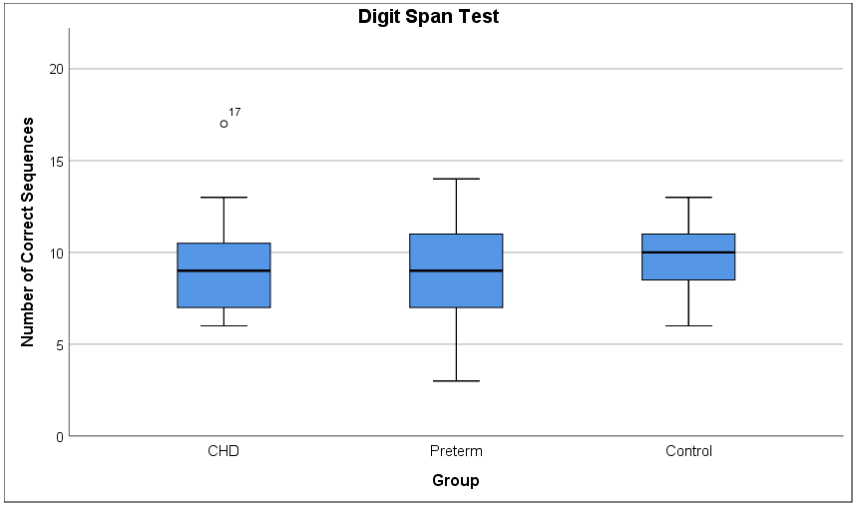

Figure A 6: Number of Correct Sequences in the Digit Span Test for each group with no significant differences between the groups

7.5 Box Plots for Non-Significant Differences in Cognitive Flexibility Performance

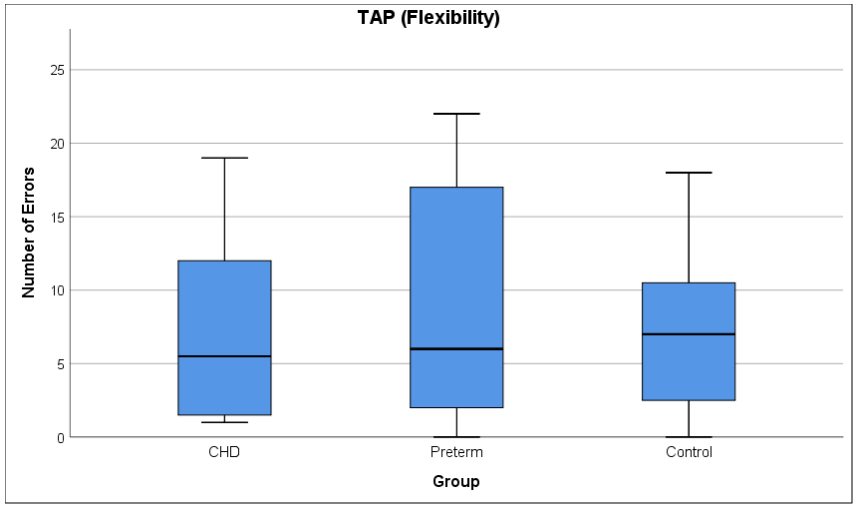

Figure A 7: Number of Errors in the Flexibility subtest of TAP for each group with no significant differences between the groups

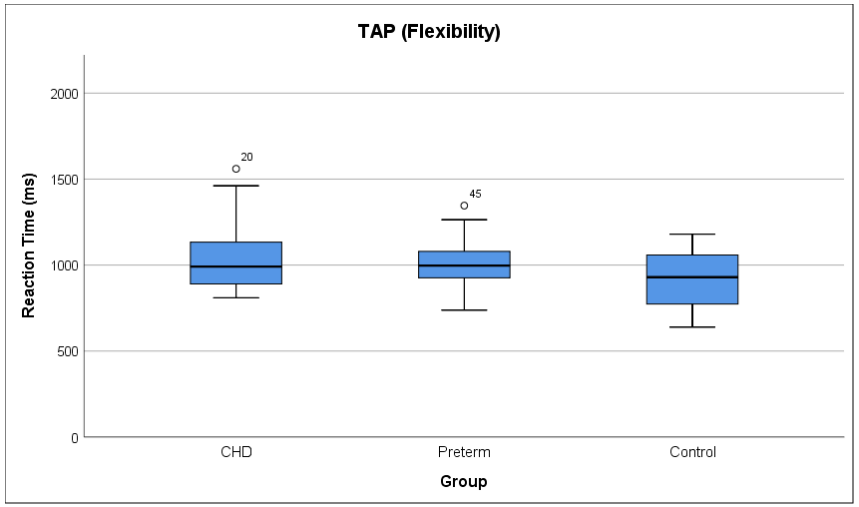

Figure A 8: Reaction Time in ms in the Flexibility subtest of TAP for each group with no significant differences between the groups

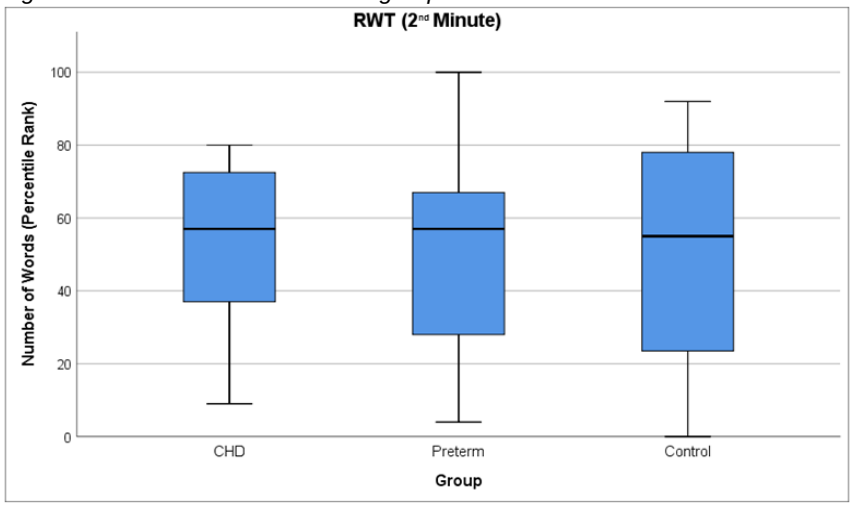

Figure A 9: Number of Words in percentile rank in the Regensburger Wortflüssigkeit-stest (RWT) for each group with no significant differences between the groups

7.6 Box Plots for Non-Significant Differences in Visual-Spatial Planning Performance

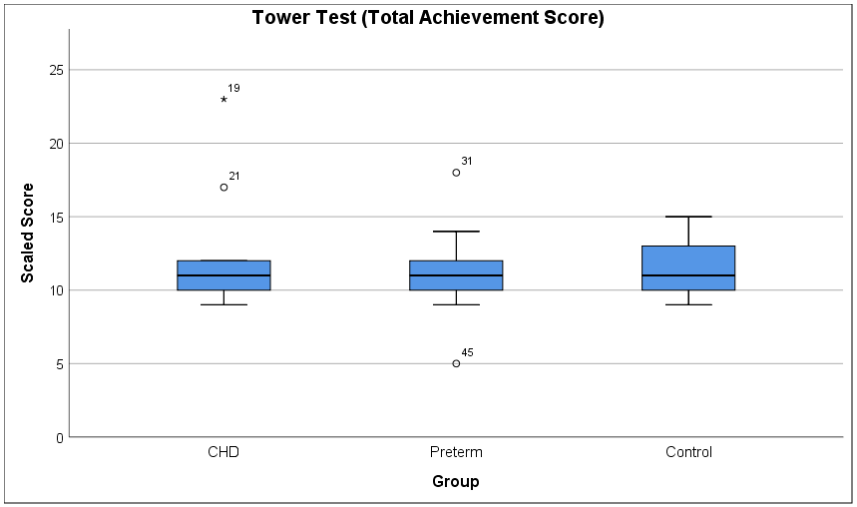

Figure A 10: Total Achievement Score (Scaled Score) in the Tower Test for each group with no significant differences between the groups

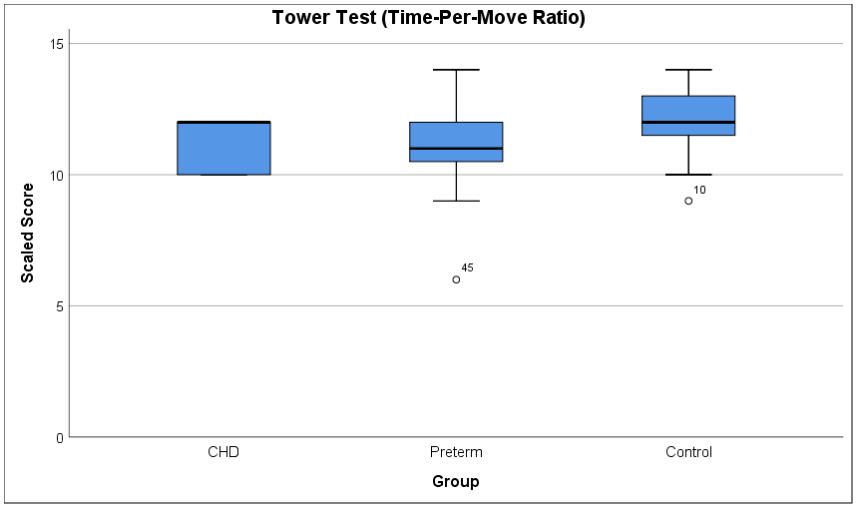

Figure A 11: Time-Per-Move-Ratio (Scaled Score) in the Tower Test for each group with no significant differences between the groups

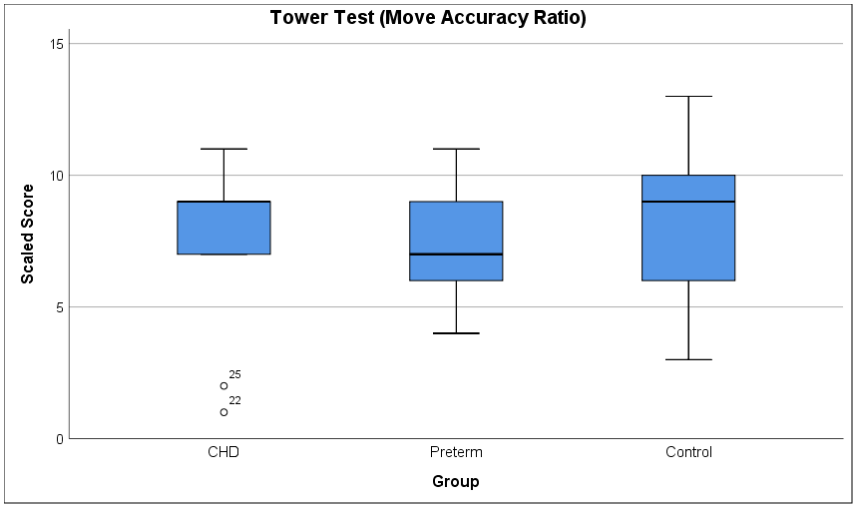

Figure A 12: Move Accuracy Ratio (Scaled Score) in the Tower Test for each group with no significant differences between the groups

7.7 Box Plots for Non-Significant Differences in Subcortical Brain Volumes

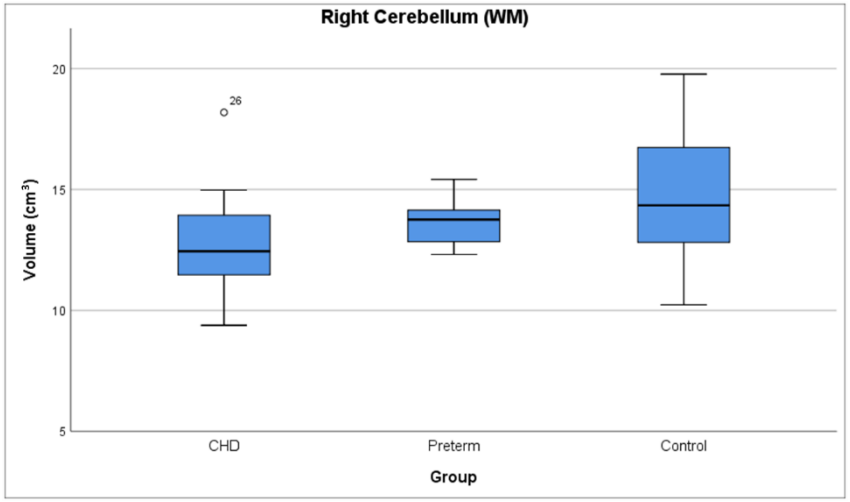

Figure A 13: Right cerebellar WM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

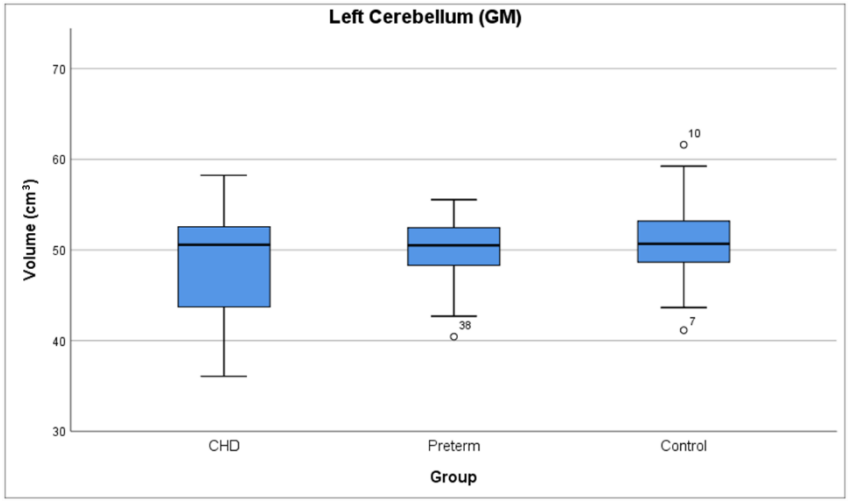

Figure A 14: Left cerebellar GM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

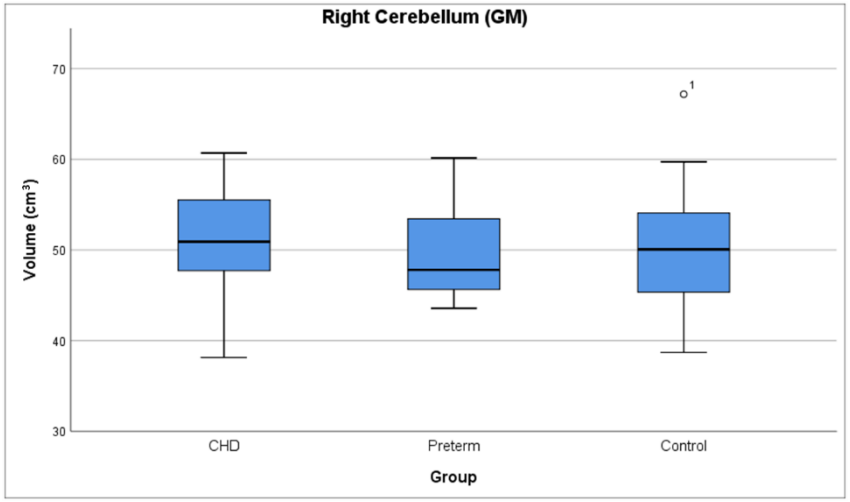

Figure A 15: Right cerebellar GM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

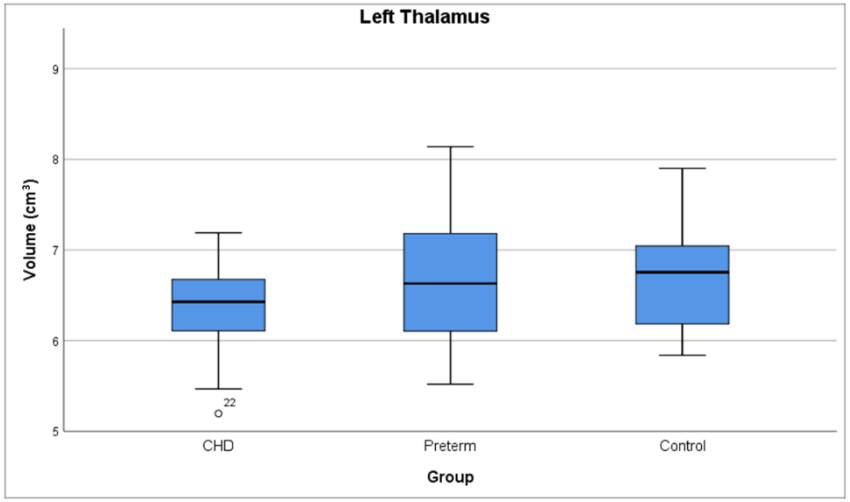

Figure A 16: *Left thalamus volume from each group with no significant differences between the groups. Volumes are reported in cm^3*

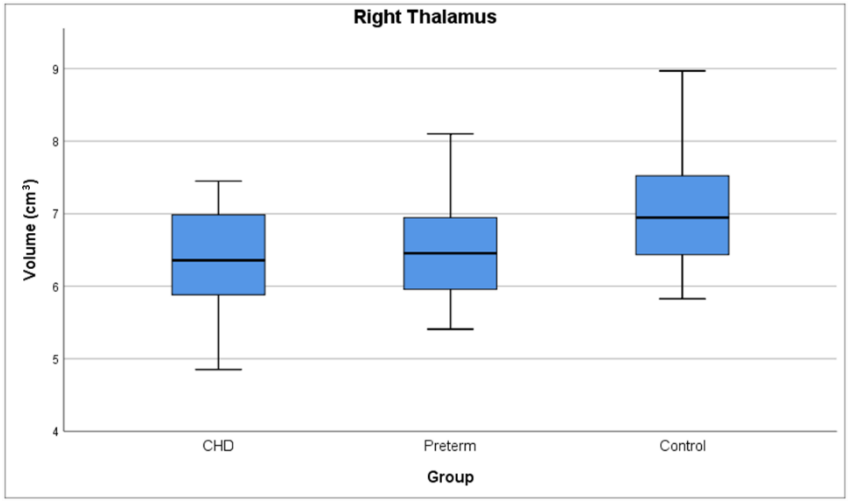

Figure A 17: Right thalamus volume from each group with no significant differences between the groups. Volumes are reported in cm^3

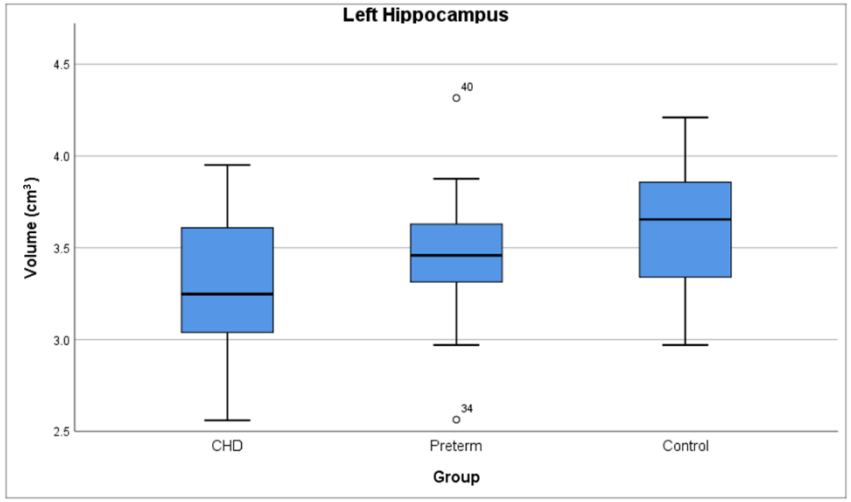

Figure A 18: Left hippocampus volume from each group with no significant differences between the groups. Volumes are reported in cm^3

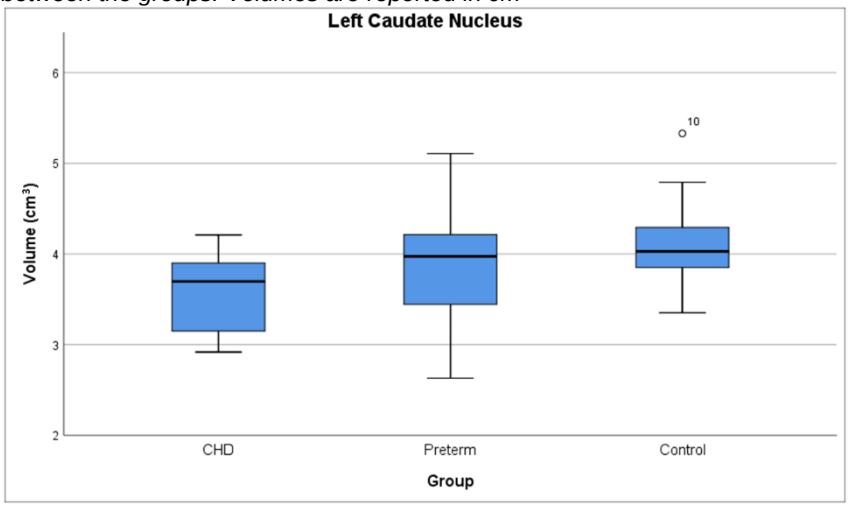

Figure A 19: Left caudate nucleus volume from each group with no significant differences between the groups. Volumes are reported in cm^3

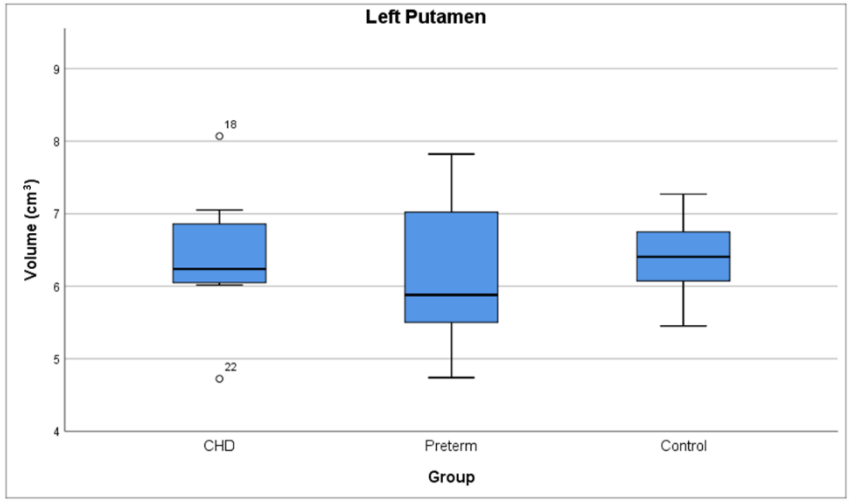

Figure A 20: Left putamen volume from each group with no significant differences between the groups. Volumes are reported in cm^3

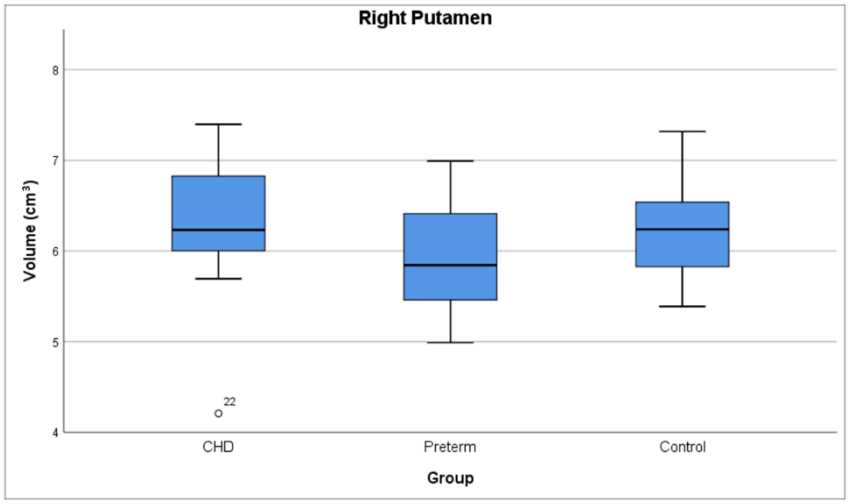

Figure A 21: Right putamen *volume from each group with no significant differences between the groups. Volumes are reported in cm³*

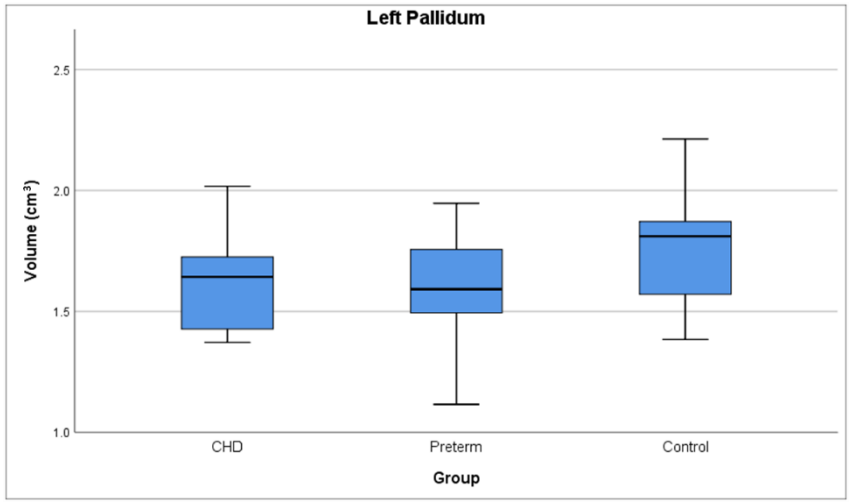

Figure A 22: Left pallidum volume from each group with no significant differences between the groups. Volumes are reported in cm³

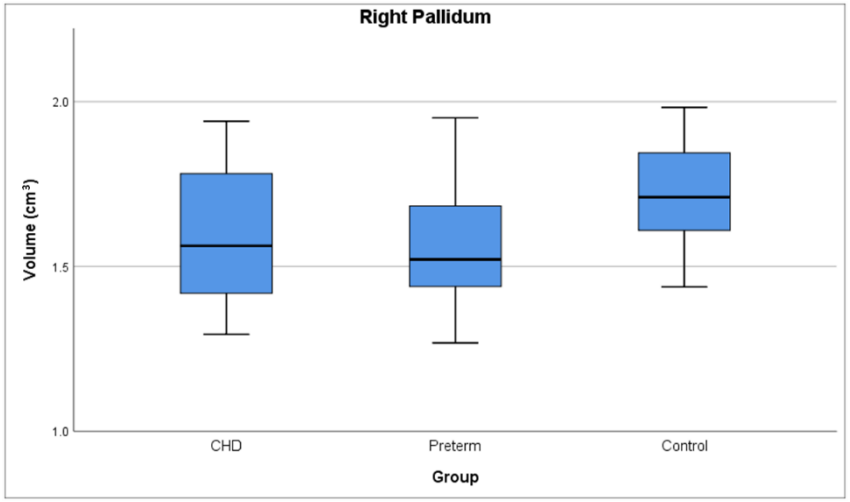

Figure A 23: Right pallidum volume from each group with no significant differences between the groups. Volumes are reported in cm³

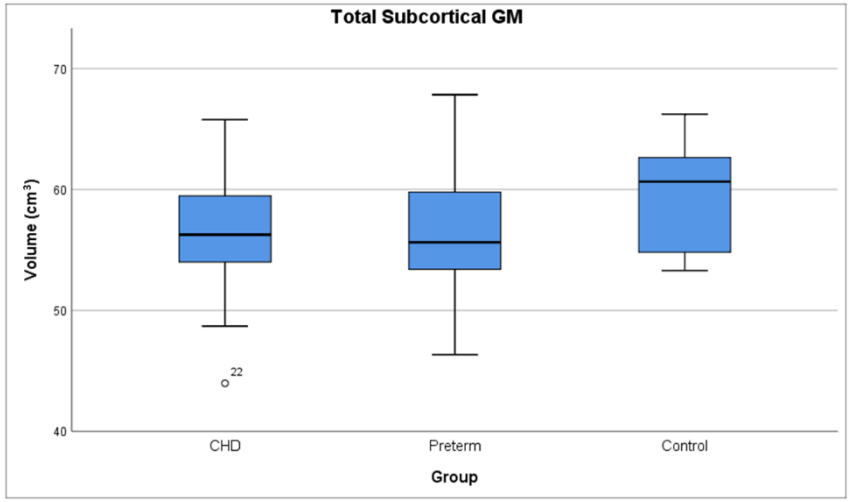

Figure A 24: Total subcortical GM *volume from each group with no significant differences between the groups. Volumes are reported in cm³*

7.8 Box Plots for Non-Significant Differences in Cortical and Total Brain Volumes

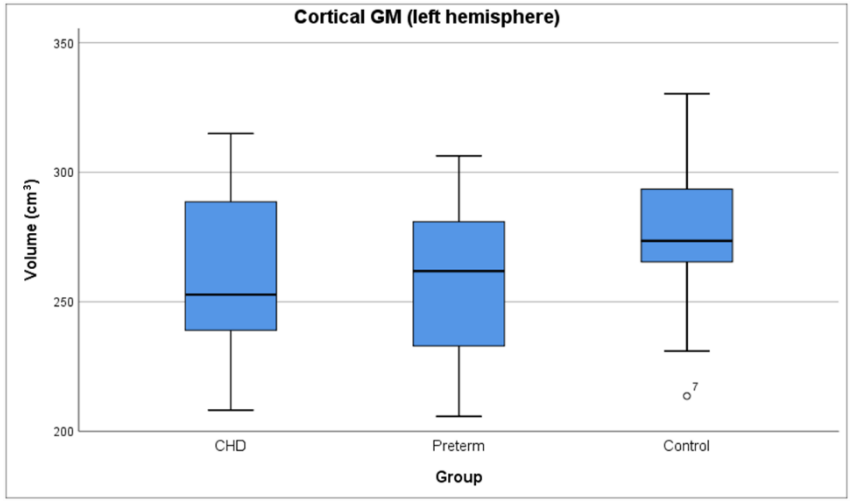

Figure A 25: Left cortical GM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

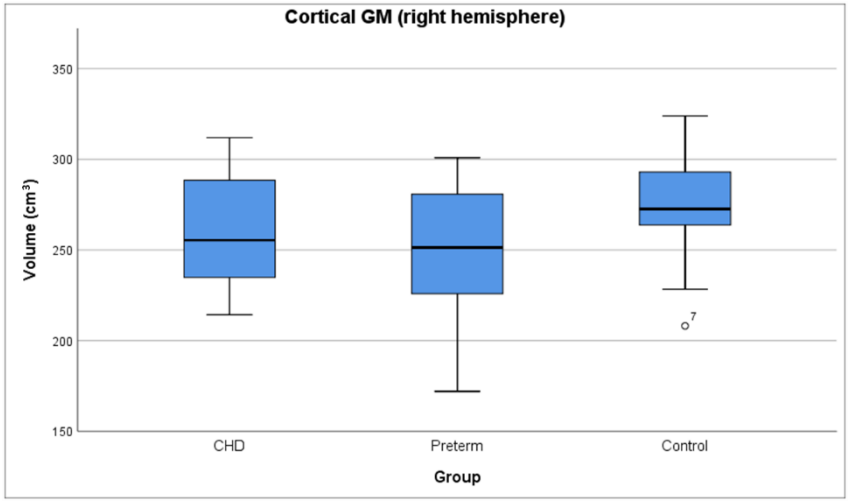

Figure A 26: Right cortical GM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

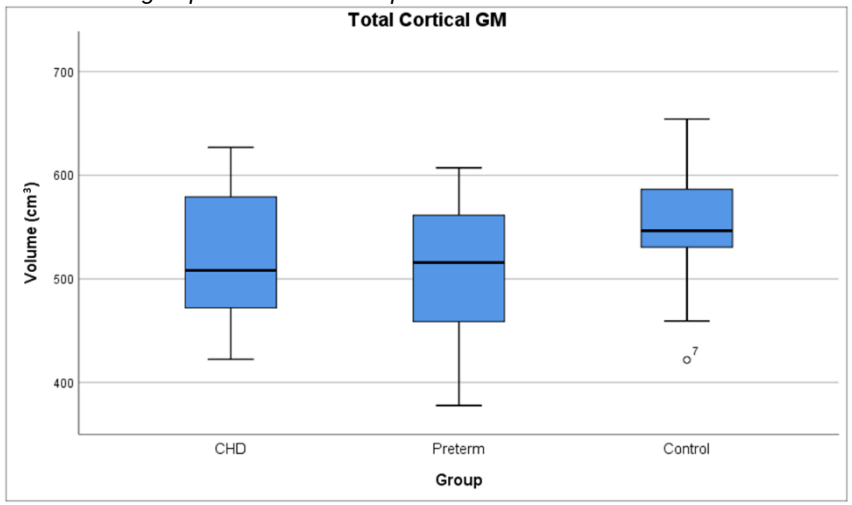

Figure A 27: Total cortical GM *volume from each group with no significant differences between the groups. Volumes are reported in cm^3*

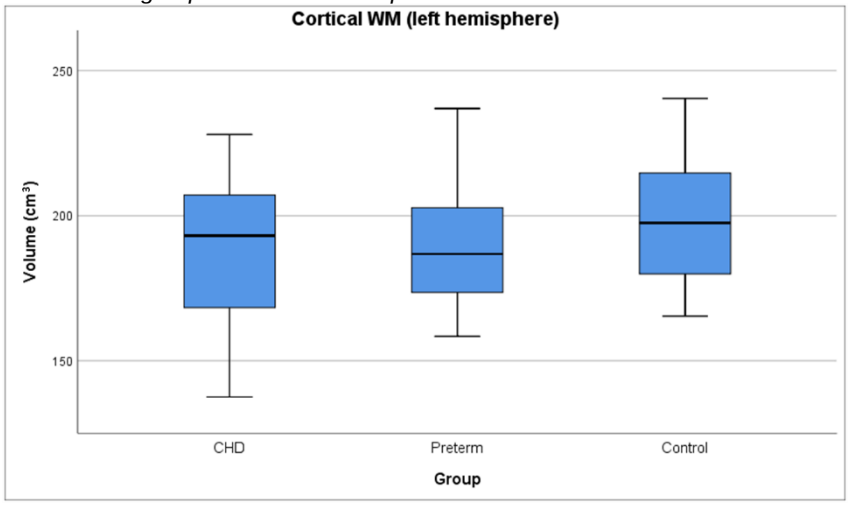

Figure A 28: Left cortical WM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

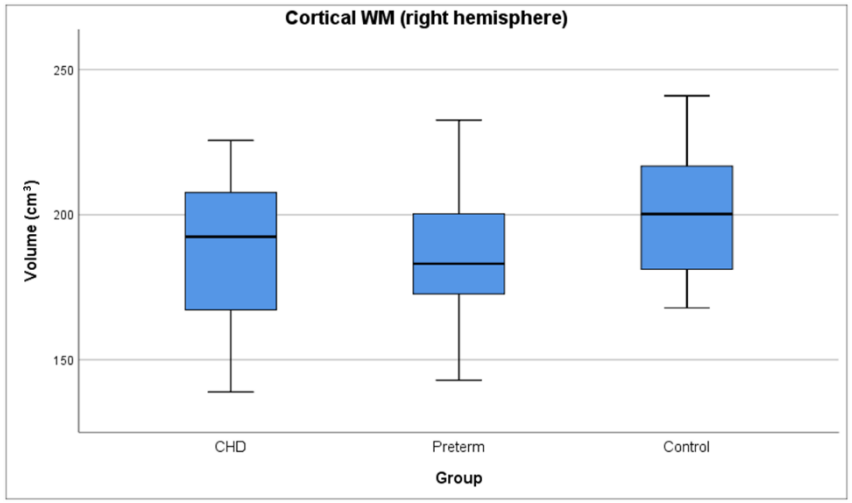

Figure A 29: Right cortical WM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

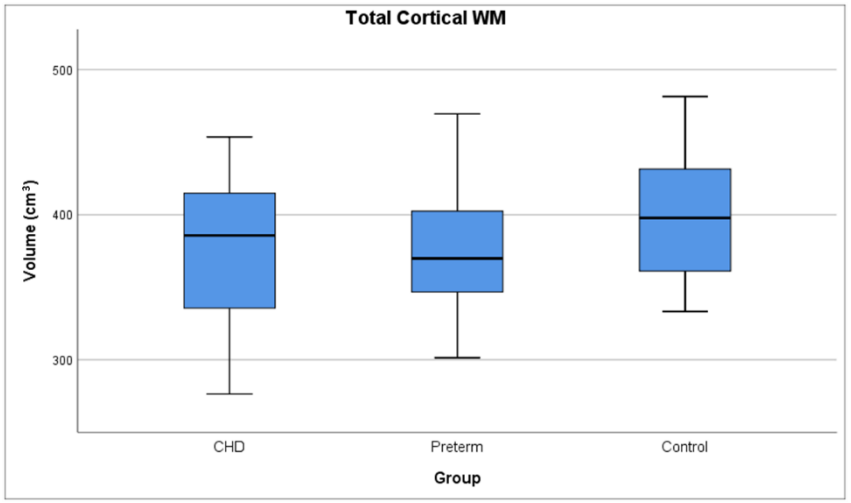

Figure A 30: Total cortical WM volume from each group with no significant differences between the groups. Volumes are reported in cm^3

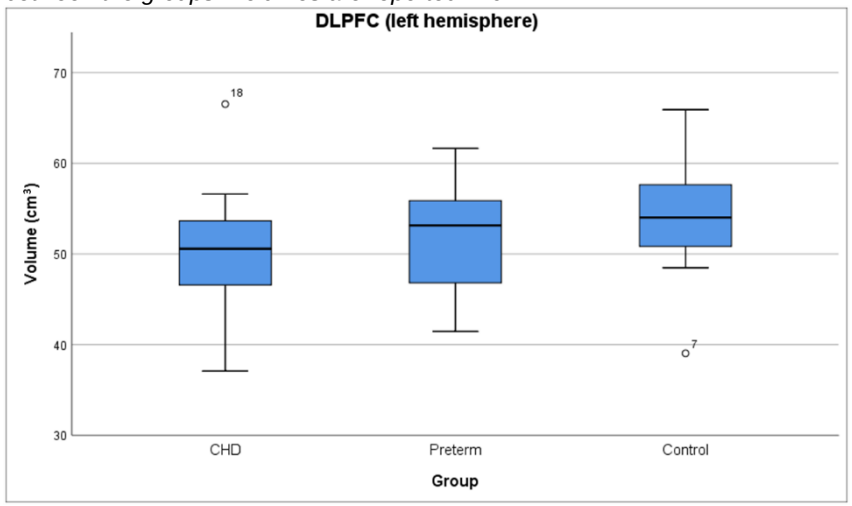

Figure A 31: Left dorsolateral prefrontal cortex volume from each group with no significant differences between the groups. Volumes are reported in cm^3

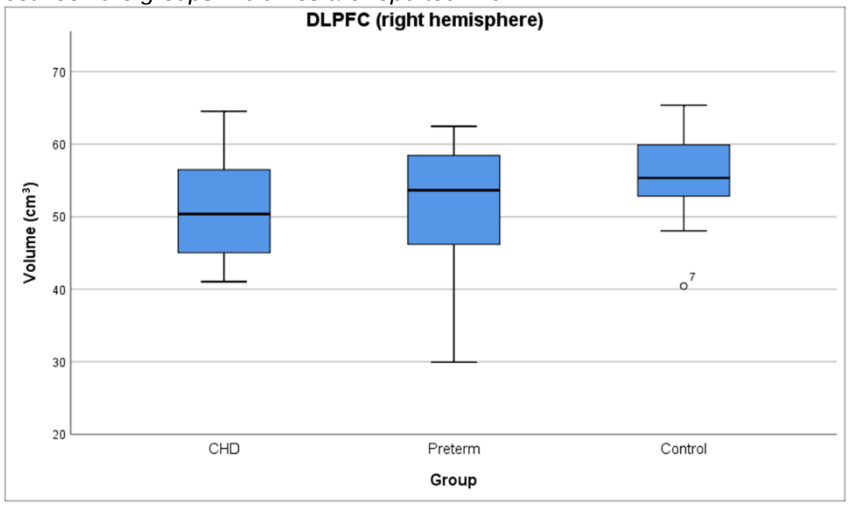

Figure A 32: Right dorsolateral prefrontal cortex volume from each group with no significant differences between the groups. Volumes are reported in cm^3

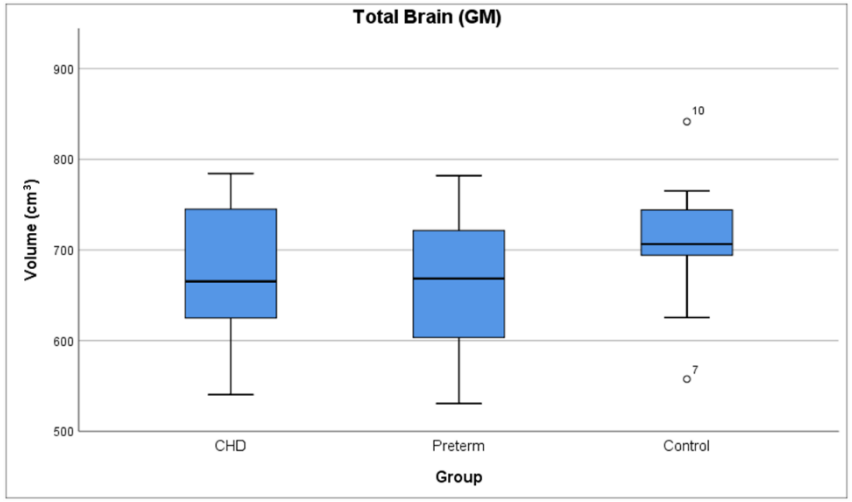

Figure A 33: Left thalamic volume from each group with no significant differences between the groups. Volumes are reported in cm^3

7.9 Correlations for the groups separately

Table A 4: Correlations of EF outcome with subcortical brain volumes in the control group

Control Group			Subcortical Brain Volumes														
			Cerebellum				Thalamus		Hippocampus		Basal Ganglia						GM
			WM Left	WM Right	GM Left	GM Right	Left	Right	Left	Right	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Pallidum Left	Pallidum Right	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.66**	.45	.27	.10	.33	.37	.43	.41	.31	.43	.36	.42	.57*	.60*	.45
		Highest Span Length (forwards)	.54*	.40	.26	.16	.28	.27	.30	.35	.34	.40	.33	.41	.56*	.52*	.39
		Number of Correct Sequences (backwards)	.39	.31	.04	-.16	.19	.31	.26	.34	.10	.16	.22	.24	.31	.31	.18
		Highest Span Length (backwards)	.34[a]	.27	.29[a]	.07[a]	.13[a]	.14[a]	.16[a]	.49[a]	-.03[a]	.01[a]	.19[a]	.18[a]	.35[a]	.13[a]	.14[a]
	TAP Working Memory	Number of Errors	-.49	-.54*	-.31	-.41	-.13	-.04	-.35	-.28	-.27	-.25	-.64**	-.70**	-.39	-.33	-.46
		Omissions	.11	.06	.28	.20	.09	-.20	-.17	.01	.14	.27	-.42	-.25	.31	-.07	-.03
	Digit Span Test	Number of Correct Sequences	.37[a]	.25	.48[a]	.23[a]	.07[a]	-.04[a]	.13[a]	.33[a]	-.06[a]	-.04[a]	.05[a]	.24[a]	.26[a]	.01[a]	.11[a]
Flexibility	TAP Flexibility	Number of Errors	-.27	-.40	.36	.25	-.19	-.16	-.17	.18	-.12	-.13	-.44	-.36	.13	.03	-.12
		Reaction Time	-.33	-.32	-.18	.07	-.28	-.44	-.31	-.37	-.15	-.11	-.41	-.37	-.20	-.39	-.38
	RWT	Number of Words, 1st Minute (Percentile Rank)	-.38	-.41	-.11	-.20	-.40	-.39	-.01	-.15	-.24	-.31	-.13	-.07	-.31	-.33	-.26
		Number of Words, 2nd Minute (Percentile Rank)	-.49[a]	-.52*	-.55*[a]	-.60*[a]	-.44[a]	-.16[a]	-.33[a]	-.53*[a]	-.20[a]	-.30[a]	-.07[a]	-.10[a]	-.37[a]	-.55*[a]	-.42[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	-.41	-.19	-.03	.20	-.55	-.74**	-.37	-.42	-.41	-.47	-.47	-.34	-.57	-.63*	-.56
		Time-Per-Move Ratio	-.66*	-.81**	-.43	-.37	-.61*	-.62*	-.10	-.44	-.36	-.50	-.43	-.34	-.63*	-.58*	-.67*
		Move Accuracy Ratio	.36	.37	.0	.26	-.16	-.22	.11	-.07	.12	.10	.13	.11	.17	-.02	.07

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

Table A 5: Correlations of EF outcome with cortical brain volumes in the control group

Control Group			Cortical Brain Volumes						Prefrontal Cortex Volumes				Total Brain Volume
			GM			WM			Ventrolateral		Dorsolateral		GM
			LH	RH	Total	LH	RH	Total	LH	RH	LH	RH	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.62*	.52*	.58*	.57*	.54*	.54*	.05	.10	.43	.35	.53*
		Highest Span Length (forwards)	.57*	.50	.56*	.50*	.47	.47	-.02	.02	.46	.35	.49
		Number of Correct Sequences (backwards)	.52*	.42	.49	.45	.41	.41	.16	.45	.38	.28	.37
		Highest Span Length (backwards)	.49[a]	.49[a]	.49[a]	.31[a]	.27[a]	.29[a]	.24[a]	.41	.43[a]	.39[a]	.48[a]
	TAP Working Memory	Number of Errors	-.07	-.06	-.09	-.03	-.05	-.05	-.21	-.01	-.04	-.07	-.09
		Omissions	.32	.32	.30	.19	.16	.16	.14	-.08	.37	.41	.33
	Digit Span Test	Number of Correct Sequences	.46[a]	.47[a]	.47[a]	.26[a]	.24[a]	.25[a]	.10[a]	.05	.47[a]	.52*[a]	.49[a]
Flexibility	TAP Flexibility	Number of Errors	-.12	-.03	-.08	-.09	-.08	-.08	-.33	-.51*	-.06	-.07	.01
		Reaction Time	-.35	-.38	-.39	-.49	-.50*	-.50*	-.06	-.31	-.28	-.17	-.34
	RWT	Number of Words, 1st Minute (Percentile Rank)	-.18	-.24	-.19	-.40	-.40	-.40	-.03	.05	-.08	-.10	-.32
		Number of Words, 2nd Minute (Percentile Rank)	-.24[a]	-.32[a]	-.28[a]	-.37[a]	-.40[a]	-.38[a]	-.14[a]	-.12	-.22[a]	-.25[a]	-.39[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	-.50	-.49	-.50	-.71**	-.71**	-.71**	.13	-.14	-.26	-.16	-.49
		Time-Per-Move Ratio	-.54	-.66*	-.60*	-.58*	-.58*	-.58*	-.47	.04	-.37	-.45	-.70*
		Move Accuracy Ratio	-.23	-.36	-.33	-.38	-.38	-.38	.39	-.43	-.44	-.24	-.32

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

Table A 6: Correlations of EF outcome with subcortical brain volumes in the children with CHD

Children with CHD			Subcortical Brain Volumes														
			Cerebellum				Thalamus		Hippocampus		Basal Ganglia						GM
			WM Left	WM Right	GM Left	GM Right	Left	Right	Left	Right	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Pallidum Left	Pallidum Right	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.27	.18	-.29	-.17	.65*	.56	.17	.40	.15	.17	.54	.43	.67*	.48	.60*
		Highest Span Length (forwards)	.16	.18	-.37	-.22	.43	.23	.02	.23	.02	.03	.35	.18	.36	.16	.33
		Number of Correct Sequences (backwards)	-.22	-.28	-.24	-.19	.39	.31	-.15	.18	-.19	-.26	.15	.01	.40	.10	.28
		Highest Span Length (backwards)	-.29[a]	-.33	-.13[a]	-.14[a]	.24[a]	.31[a]	-.05[a]	.23[a]	-.39[a]	-.40[a]	-.05[a]	-.05[a]	.15[a]	-.03[a]	.09[a]
	TAP Working Memory	Number of Errors	-.21	-.19	-.09	-.16	-.38	-.04	.05	-.10	-.26	-.12	-.36	-.23	-.06	-.12	-.28
		Omissions	.35	.31	.15	.14	-.05	.10	.20	.05	.18	.51	-.04	.14	.17	.30	.13
	Digit Span Test	Number of Correct Sequences	.25[a]	.64	.22[a]	.08[a]	.50[a]	.27[a]	.41[a]	.20[a]	.17[a]	.28[a]	.49[a]	.56[a]	.06[a]	.19[a]	.42[a]
Flexibility	TAP Flexibility	Number of Errors	-.33	-.52	-.27	-.39	-.48	-.40	-.40	-.50	.11	-.12	-.60*	-.54	-.16	-.32	-.49
		Reaction Time	-.35	-.36	-.36	-.40	-.56	-.76**	-.60*	-.69*	-.13	-.21	-.67*	-.72**	-.59*	-.69*	-.64*
	RWT	Number of Words, 1st Minute (Percentile Rank)	-.64*	-.34	-.06	-.11	-.13	-.46	-.35	-.23	-.11	-.34	-.57	-.45	-.76**	-.68*	-.42
		Number of Words, 2nd Minute (Percentile Rank)	-.54[a]	-.26	-.35[a]	-.35[a]	-.14[a]	-.46[a]	-.13[a]	-.08[a]	-.19[a]	-.38[a]	-.20[a]	-.26[a]	-.70*[a]	-.66*[a]	-.33[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	.06	-.34	.29	.25	.26	.48	-.43	-.11	-.03	.13	.45	.58	.50	.47	.33
		Time-Per-Move Ratio	.02	.02	.28	.32	-.61	-.22	-.26	-.28	-.48	-.56	.34	-.22	.04	-.28	-.47
		Move Accuracy Ratio	.45	.38	.65	.65	.38	-.17	-.11	-.15	.61	.61	.39	.59	-.21	.24	.28

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

Table A 7: Correlations of EF outcome with cortical brain volumes in the group of children with CHD

Children with CHD			Cortical Brain Volumes						Prefrontal Cortex Volumes				Total Brain Volume
			GM			WM			Ventrolateral		Dorsolateral		GM
			LH	RH	Total	LH	RH	Total	LH	RH	LH	RH	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.48	.34	.38	.65*	.64*	.65*	.28	.13	.32	.29	.38
		Highest Span Length (forwards)	.23	.06	.12	.44	.39	.43	.06	-.05	.0	-.02	.12
		Number of Correct Sequences (backwards)	.11	-.07	.03	.33	.25	.29	-.11	-.30	-.08	-.07	.01
		Highest Span Length (backwards)	-.08[a]	-.17[a]	-.12[a]	.24[a]	.20[a]	.22[a]	-.06[a]	-.28	-.20[a]	-.19[a]	-.12[a]
	TAP Working Memory	Number of Errors	-.40	-.33	-.34	-.33	-.26	-.33	-.46	-.45	-.25	-.13	-.38
		Omissions	-.03	.07	.04	.11	.16	.12	-.01	-.10	.14	.19	.02
	Digit Span Test	Number of Correct Sequences	.52[a]	.47[a]	.50[a]	.35[a]	.35[a]	.35[a]	.33[a]	.38	.32[a]	.31[a]	.48[a]
Flexibility	TAP Flexibility	Number of Errors	-.55	-.40	-.47	-.48	-.44	-.48	-.55	-.53	-.40	-.34	-.47
		Reaction Time	-.66*	-.61*	-.64*	-.57	-.66*	-.60*	-.51	-.49	-.64*	-.71*	-.63*
	RWT	Number of Words, 1st Minute (Percentile Rank)	-.32	-.42	-.40	-.60*	-.66*	-.62*	-.28	-.27	-.52	-.42	-.40
		Number of Words, 2nd Minute (Percentile Rank)	-.33[a]	-.35[a]	-.34[a]	-.45[a]	-.51[a]	-.48[a]	-.09[a]	-.26	-.32[a]	-.39[a]	-.37[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	.52	.49	.52	.25	.38	.34	.38	.42	.60	.39	.52
		Time-Per-Move Ratio	-.24	-.34	-.24	-.09	-.09	-.09	-.22	-.07	-.32	-.52	-.24
		Move Accuracy Ratio	.67*	.72*	.67*	.07	.15	.17	.76*	.81**	.66	.50	.67*

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

Table A 8: Correlations of EF outcome with subcortical brain volumes in the group of very preterm children

Very Preterm Children			Subcortical Brain Volumes														
			Cerebellum				Thalamus		Hippocampus		Basal Ganglia						GM
			WM Left	WM Right	GM Left	GM Right	Left	Right	Left	Right	Caudate Left	Caudate Right	Putamen Left	Putamen Right	Pallidum Left	Pallidum Right	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	-.02	.10	.13	.25	-.12	-.27	.40	.44	-.05	.09	.54*	.54*	.08	.42	.25
		Highest Span Length (forwards)	-.19	-.03	.21	.17	.08	-.17	.43	.40	-.09	.04	.58*	.60*	.12	.38	.34
		Number of Correct Sequences (backwards)	.26	.27	-.03	.23	.20	.15	.48	.51*	.12	.24	.47	.42	.50*	.62*	.42
		Highest Span Length (backwards)	.31[a]	.23	-.05[a]	.15[a]	.22[a]	.14[a]	.36[a]	.51*[a]	.12[a]	.24[a]	.59*[a]	.49[a]	.45[a]	.59*[a]	.44[a]
	TAP Working Memory	Number of Errors	.10	-.09	.05	-.17	.08	.33	-.11	-.21	.19	.08	-.19	-.34	.07	-.20	-.01
		Omissions	.20	-.02	-.05	.0	-.08	-.19	-.13	-.19	.09	.10	-.32	-.11	-.31	-.27	-.13
	Digit Span Test	Number of Correct Sequences	.17[a]	.06	.43[a]	.48[a]	.17[a]	-.04[a]	.42[a]	.44[a]	.16[a]	.22[a]	.52*[a]	.57*[a]	.38[a]	.40[a]	.41[a]
Flexibility	TAP Flexibility	Number of Errors	.04	-.24	-.35	-.35	.17	.26	-.18	-.31	-.49	-.46	-.05	-.14	-.22	-.29	-.07
		Reaction Time	-.12	-.01	.42	.24	.04	.04	-.09	-.29	-.08	-.23	-.34	-.14	-.22	-.34	-.14
	RWT	Number of Words, 1st Minute (Percentile Rank)	.07	.52*	.27	.33	-.09	-.14	-.08	-.05	.05	-.01	-.23	-.21	.02	-.15	-.11
		Number of Words, 2nd Minute (Percentile Rank)	.20[a]	.35	.29[a]	.23[a]	-.41[a]	-.40[a]	-.35[a]	-.25[a]	-.25[a]	-.23[a]	-.37[a]	-.41[a]	-.28[a]	-.34[a]	-.44[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	.44	.26	-.16	.40	-.17	-.24	.04	-.12	.09	.07	.01	.00	.00	-.14	-.05
		Time-Per-Move Ratio	.40	.18	-.05	.13	.43	.22	.30	.33	.17	.21	.39	.40	.46	.37	.41
		Move Accuracy Ratio	-.10	.08	-.24	.07	.15	.09	.26	.14	.32	.29	.15	.15	.42	.23	.24

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

Table A 9: Correlations of EF outcome with cortical brain volumes in the group of very preterm children

Very Preterm Children			Cortical Brain Volumes						Prefrontal Cortex Volumes				Total Brain Volume
			GM			WM			Ventrolateral		Dorsolateral		GM
			LH	RH	Total	LH	RH	Total	LH	RH	LH	RH	Total
Working Memory	Corsi Block Tapping Task	Number of Correct Sequences (forwards)	.71**	.73**	.73**	.71**	.66**	.66**	.68**	.83**	.55*	.67**	.71**
		Highest Span Length (forwards)	.64**	.66**	.66**	.75**	.66**	.68**	.56*	.72**	.55*	.60*	.65**
		Number of Correct Sequences (backwards)	.60*	.54*	.54*	.55*	.55*	.55*	.30	.52*	.57*	.66**	.53*
		Highest Span Length (backwards)	.66**[a]	.67**[a]	.67**[a]	.64**[a]	.70**[a]	.68**[a]	.33[a]	.54*	.67**[a]	.76**[a]	.67**[a]
	TAP Working Memory	Number of Errors	-.35	-.46	-.46	-.28	-.32	-.33	-.21	-.29	-.51*	-.49	-.43
		Omissions	-.15	-.02	-.02	-.33	-.28	-.26	-.29	-.39	-.16	-.07	-.04
	Digit Span Test	Number of Correct Sequences	.59*[a]	.58*[a]	.59*[a]	.60*[a]	.60*[a]	.60*[a]	.51*[a]	.65**	.44[a]	.45[a]	.64**[a]
Flexibility	TAP Flexibility	Number of Errors	-.34	-.28	-.28	-.25	-.16	-.17	-.32	-.47	-.22	-.13	-.29
		Reaction Time	-.56*	-.54*	-.54*	-.31	-.37	-.34	-.38	-.45	-.54*	-.65**	-.47
	RWT	Number of Words, 1st Minute (Percentile Rank)	.04	.02	.02	-.05	-.03	-.06	.34	.25	-.20	-.15	.02
		Number of Words, 2nd Minute (Percentile Rank)	-.12[a]	.05[a]	-.03[a]	-.14[a]	-.03[a]	-.08[a]	.17[a]	.31	-.26[a]	.03[a]	-.03[a]
Visual-Spatial Planning	Tower Test	Total Achievement Score	-.02	-.02	-.02	-.11	-.17	-.17	-.04	.15	-.14	-.05	-.06
		Time-Per-Move Ratio	.30	.31	.31	.23	.29	.30	-.02	-.05	.43	.41	.32
		Move Accuracy Ratio	.28	.16	.16	.29	.21	.21	.18	.26	.27	.09	.16

TAP: Testbatterie zur Aufmerksamkeitsprüfung, RWT: Regensburger Wortflüssigkeitstest, WM: white matter, GM: grey matter

[a]Pearson's r, Spearman's r if not special labeled, *** $p < .001$, ** $p < .01$, * $p < .05$

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Zürich, 01. Oktober 2018
Ort und Datum


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